Appeal Nos. 2016-1619, -1621, -1763, -1764

United States Court of Appeals

for the

Federal Circuit

SUPERNUS PHARMACEUTICALS, INC.,

Plaintiff-Cross-Appellant,

– v. –

ACTAVIS INC., WATSON LABORATORIES, INC. - FLORIDA N/K/A ACTAVIS LABORATORIES FL, INC., ACTAVIS PHARMA, INC., WATSON LABORATORIES, INC., and ANDA, INC.,

Defendants-Appellants.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY IN CASE NOS. 13-CV-04740-RMB-JS AND 14-CV-01981-RMB-JS, HONORABLE RENEE MARIE BUMB

NON-CONFIDENTIAL BRIEF FOR DEFENDANTS-APPELLANTS

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FORM 9. Certificate of Interest

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Supernus Pharmaceuticals, Inc. v. Actavis Inc.

Case No. 16-1619;16-1621

CERTIFICATE OF INTEREST

Counsel for the (petitioner) (**appellant**) (respondent) (appellee) (amicus) (name of party) certifies the following (use "None" if applicable; use extra sheets if necessary):

1. The full name of every party or amicus represented by me is:

Actavis Inc.,Watson Laboratories, Inc. - Florida n/k/a Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Watson Laboratories, Inc., and Anda, Inc.

2. The name of the real party in interest (Please only include any real party in interest NOT identified in Question 3. below) represented by me is:

Actavis Inc.,Watson Laboratories, Inc. - Florida n/k/a Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Watson Laboratories, Inc., and Anda, Inc.

3. All parent corporations and any publicly held companies that own 10 percent of the stock of the party or amicus curiae represented by me are listed below. (Please list each party or amicus curiae represented with the parent or publicly held company that owns 10 percent or more so they are distinguished separately.)

Allergan plc

4. [X] The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

Holland & Knight LLP, 31 West 52nd Street, New York, NY 10019: Charles A. Weiss, Howard S. Suh, Michael B. Eisenberg, Eric H. Yecies, Christopher M. Scott, Nicholas P. Chiara, Leslie Kushner

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March 4, 2016
Date

/s/ Charles A. Weiss
Signature of counsel

Please Note: All questions must be answered

Charles A. Weiss
Printed name of counsel

cc: Counsel of Record

Reset Fields

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CONFIDENTIAL MATERIAL OMITTED

The material redacted from this brief is subject to a protective order. The confidential information on page 50 relates to a document, and/or testimony regarding that document, which has been designated as confidential.

The material redacted on pages Appx33-40, Appx49-50, Appx53, Appx59, Appx61-73, Appx76-79, Appx82, and Appx85-91 was redacted by the district court in the publicly filed Opinion, subject to a protective order, and relates to the specific components of a formulation, the specific method of manufacture, technical papers or documents which have been designated as confidential, and/or testimony regarding those documents.

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STATUTES

INDEX OF ABBREVIATIONS

ABBREVIATION	REFERENCE
’898 Patent	United States Patent No. 7,722,898
’131 patent	United States Patent No. 7,910,131
’600 patent	United States Patent No. 8,617,600
ANDA	Actavis Abbreviated New Drug Application #205444
Actavis	Defendants-Appellants Actavis Inc., Watson Laboratories, Inc. – Florida n/k/a Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Watson Laboratories, Inc., and Anda, Inc.
Appx	Joint Appendix
C_{max}	concentration maximum
C_{min}	concentration minimum
C_{24}	concentration at 24 hours
D.I.	Docket index number, 13-4740 or 14-1981, United States District Court District of New Jersey (unless noted otherwise)
FDA	U.S. Food and Drug Administration
HPMC	hydroxypropyl methylcellulose, also referred to by the common name hypromellose or the brand name Methocel (often followed by a grade number, *e.g.*, HPMC K4M)
Jazz	Jazz Pharmaceuticals
MCC	Microcrystalline Cellulose
PVP	polyvinyl pyrrolidone, also referred to by the common name povidone or the brand name Kollidon, (often followed by a grade number, *e.g.*, PVP-K90)
POSA	person of ordinary skill in the art
SSCI	SSCI Inc. (Solid State Chemical Information)
Shire	Shire Laboratories
Supernus	Plaintiff-Appellee Supernus Pharmaceuticals, Inc.,
SLS	sodium lauryl sulfate

STATEMENT OF RELATED CASES

There has been and is no other appeal from the present civil action in this or any other appellate court.

Plaintiff has asserted the patents at issue here in *Supernus Pharms. v. TWi Pharm.*, 1:15-cv-00369-RMB-JS (D.N.J.). Counsel is unaware of any other case pending in this or any other court that will directly affect, or will be directly affected by, the decision in this present appeal.

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). On February 5, 2016, the district court issued its opinion (Appx4-139), and on February 18, 2016, it entered final judgment (Appx140-143).

Defendants-Appellants (collectively, "Actavis") timely filed the notice of appeal on February 19, 2016.

This Court has jurisdiction over the appeal pursuant to 28 U.S.C. §§ 1291 and 1295(a)(1).

STATEMENT OF THE ISSUES

Whether the district court's finding of infringement should be reversed where:

1. the court did not apply the construction of "homogeneous matrix" it provided at *Markman*—a matrix in which all the ingredients were "uniformly dispersed"—and effectively adopted an erroneous construction under which this claim element equated to compliance with FDA standards that (i) were not part of the intrinsic evidence, (ii) concern manufacturing and quality control matters that are different from the structural requirement of the claim element, and (iii) cannot in any event support a finding that this element was present when the only direct evidence on the issue—Raman images of the Actavis tablets that actually showed the arrangement of ingredients within the tables—plainly demonstrated that the ingredients in the Actavis tablets were not uniformly dispersed; and

2. the court applied an incorrect claim construction and erred in concluding that an excipient in the Actavis tablets qualified as an "agent that enhances the solubility of oxcarbazepine" based on legally irrelevant testing which showed only that vastly greater amounts of that excipient enhanced the solubility of oxcarbazepine in water, and despite statements in the specification and trial testimony of the inventor that this very excipient did not serve the claimed purpose.

Whether the district court erroneously rejected Actavis's invalidity defenses under Section 112 where:

1. it applied an incorrect standard to the written-description defense by evaluating it as a question of enablement and obviousness;

2. it applied an incorrect standard to the indefiniteness defense by similarly evaluating it as a question of enablement.

STATEMENT OF THE CASE

In this Hatch-Waxman Act case, plaintiff Supernus Pharmaceuticals, Inc. ("Supernus") sued Actavis for infringement of U.S. Patent Nos. 7,722,898 (the "'898 patent"), 7,910,131 (the "'131 patent"), and 8,617,600 (the "'600 patent") based on submission of an ANDA with a Paragraph IV certification that sought approval for extended-release oxcarbazepine tablets, generic to the reference-listed drug Oxtellar XR. (Appx289, Appx299 ¶36, Appx300 ¶41 (case no. 1:13-cv-04740-RMB-JS, D.I. 1); Appx398, Appx408 ¶5 (case no. 1:14-cv-01981-RMB-JS, D.I. 1); Appx14322).

The district court construed several disputed claim terms. (Appx2481-82; Appx2742-43; Appx2744-45.) After a bench trial, it held that the ANDA product infringed the asserted claims of the '898 patent and '131 patent, did not infringe the asserted claims of the '600 patent, and rejected Actavis' invalidity defenses. (Appx9; Appx141-42).

After Actavis appealed and Supernus cross-appealed, the parties resolved all claims concerning the '600 patent, and filed a joint motion reflecting that (Document 33, filed 5/4/2016). Accordingly, this appeal now concerns only the '898 patent and '131 patent.

STATEMENT OF THE FACTS

This case concerns extended-release formulations of oxcarbazepine, an anti-epileptic drug first approved in the U.S. in 2000 as the Novartis product "Trileptal." (Appx13155-56 1241:11-1242:1; Appx25547,52). Trileptal was an immediate-release product labelled for twice-daily use. (Appx12998 1084:6-15; Appx25551).

Supernus obtained FDA approval for Oxtellar, an extended-release formulation labelled for once-daily use, in October 2012. (Appx14341). Actavis subsequently submitted an ANDA with a Paragraph IV certification. (Appx14322; Appx11689 ¶19). This case followed.

I. The Patents-In-Suit

The patents-in-suit are related as continuations, with the '898 patent the first to issue, followed by the '131 patent. (Appx220; Appx243). Claim 1 of the '898 patent is exemplary:

> A pharmaceutical formulation for once-a-day administration of oxcarbazepine comprising a homogeneous matrix comprising:
>
> (a) oxcarbazepine;
>
> (b) a matrix-forming polymer selected from the group consisting of . . . .;
>
> (c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of . . .; and

> (d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of . . . .

(Appx240 12:50-13:6).[1]

A. The Claim Element "Homogeneous Matrix" Was Added By Amendment To Overcome Prior-Art Rejections

During prosecution of the parent application, Supernus added the term "matrix" to overcome rejections based in part on prior-art in which the excipients varied between the tablet's core and coating. (Appx14053; Appx14058-14061). The Examiner maintained the rejection, explaining that Supernus' addition of "matrix" was insufficient because it did not limit the claims to "a homogeneously admixed mixture of the four components." (Appx14072).

In response, Supernus further amended to add "homogeneous," with all claims now requiring a "homogeneous matrix" of the four recited elements. (Appx14086; Appx14089 ¶4).

B. Construction Of "Homogeneous Matrix"

The district court construed "homogeneous matrix" to mean a "matrix in which the ingredients or constituents are uniformly dispersed" (Appx2744 ¶1), rejecting Supernus' construction of "a substantially uniform dispersion of one or more constituents in a given volume," later explaining in its post-trial Opinion that

[1] The members of the *Markush* groups for elements (b), (c), and (d) are elided because they are not important to the issues on appeal.

Supernus' construction would read "matrix" out of the claims, and observing that the qualifier "substantially" had "no support in the intrinsic evidence" (Appx21-22). The district court's *Markman* order, however, contained no explanation of the court's reasoning or elucidation of the construction. (Appx 2742; Appx2744).

II. The Actavis Tablets Lack A "Matrix In Which The Ingredients Or Constituents Are Uniformly Dispersed"

The evidence at trial included Raman images, captured by both sides' experts, of an Actavis tablet that showed the spatial distribution of the tablet's several ingredients. (Appx23218-36; Appx12234-37 320:10-323:3; Appx12246-47 332:19-333:1; Appx12811-13 897:20-899:18; Appx12807 893:18-25; Appx12818-23 904:14-906:6, 908:3-909:4, discussing Appx25744-86). The Raman images and optical micrograph made by Supernus' expert, Dr. Bugay, showed a non-uniform distribution of ingredients in that tablet, as did the Raman images and Near-infrared spectroscopy of Actavis' expert, Dr. Muzzio. (Appx23218-36; Appx12810-11 896:6-897:19, referring to Appx23231; Appx12814 900:1-25, referring to Appx23219; Appx12816 902:8-20, referring to Appx23225; Appx12293-95 379:23-381:1, referring to Appx23232; Appx12333 419:22-25; Appx12807 893:18-25; Appx12818-28 904:14-906:6, 908:3-909:4, referring to Appx25744-86, 911:15-914:2, referring to Appx25715-30). Some were more densely present on one side. (Appx12814 900:1-25, referring to Appx23219; Appx12816 902:8-20, referring to Appx23225). Also shown were

agglomeration of ingredients, separated by regions in which they were absent. (Appx12810-11 896:6-897:19, referring to Appx23231; Appx12814 900:1-25, referring to Appx23219; Appx12816 902:8-20, referring to Appx23225; Appx12293-95 379:23-381:1, referring to Appx23232; Appx12333 419:22-25). The scientific literature described such pharmaceutical formulations as not uniform and not homogeneous. (Appx25920 ¶1, Appx25921 Fig.3A; Appx25913 ¶3, Appx25914 Fig.7).

III. The Patents And The Inventor Indicate That PVP-K90 Is Not The Claimed "Agent That Enhances The Solubility Of Oxcarbazepine"

All asserted claims required "an agent that enhances the solubility of oxcarbazepine," which the district court found was satisfied by polyvinyl pyrrolidone ("PVP") K90 present in the Actavis tablets at less than 0.5% by weight. PVP-K90 is a high molecular-weight grade of PVP, with an average molecular weight of approximately 1,000,000. (Appx22940; Appx25822 Table 1).[2] The specification of the patents-in-suit, however, identifies only "low molecular weight" PVP as one of the preferred solubility enhancers, and reports that an intermediate-weight grade (K17, approximate molecular weight 10,000), actually decreased the solubility of oxcarbazepine. (Appx237 5:14-16; Appx239 10:1-31; Appx25822 Table 1; Appx13289 1376:7-20). It also characterized exemplary unsuccessful formulations with PVP-K25 (approximate molecular

[2] PVP is also referred to as "povidone" and by the brand name "Kollidon."

weight 30,000) and PVP-K90 as lacking a solubility enhancer. (Appx239-40 10:55-11:15, showing CR formulation; Appx236 3:14-19, describing Example 4 formulations; Appx239 9:10-37, showing formulations; Appx235 2:60-64, describing Example 1 formulations; Appx25822 Table 1). The inventor, Dr. Bhatt, confirmed at trial that these formulations, in Example 1 of the specification, lacked a solubility enhancer, and that he had suggested adding a solubility enhancer to them. (Appx12039 125:1-11; Appx12025 111:7-14).

SUMMARY OF THE ARGUMENT

I. The district court erred in finding that the Actavis tablets comprised a "homogeneous matrix" as required by all asserted claims. Supernus added this element during prosecution in response to a rejection that the claims were not "limited to a homogeneously admixed mixture" of the four specified components (the drug plus three excipients). (Appx14072). At the *Markman* stage, the district court rejected Supernus' proposed construction—"a substantially uniform dispersion of one or more constituents in a given volume"—and provided a construction that on its face appeared correct, *i.e.*, "a matrix in which the ingredients or constituents are uniformly dispersed." (Appx2744 ¶1).

Consistent with this construction, Actavis relied at trial on Raman images of its accused tablets—images made by Supernus' own infringement expert—that plainly showed the ingredients were not "uniformly dispersed." Because the district court failed to apply the correct claim construction, it treated the images as largely irrelevant—even though it was the only direct evidence on the question posed by the *Markman*-stage construction, *i.e.*, the physical/spatial distribution of ingredients within the Actavis tablets—and erred legally in determining this element was satisfied because the Actavis tablets were made in accordance with good manufacturing practices and satisfied FDA regulatory standards.

II. The district court erred in its application of construction of the term "agent that enhances the solubility of oxcarbazepine" and thus in finding that the trace amount of a binder in the Actavis tablets was the claimed "agent that enhances the solubility of oxcarbazepine" based on a test showing that an order-of-magnitude greater amount increased the solubility of oxcarbazepine in a buffer, even though the expert who ran the test admitted that it did not show what the excipient did in the Actavis tablet.

III. When Supernus amended its claims to add "homogeneous matrix," it pointed to two sections of the specification for support. Actavis's expert testified that one addressed something different, and Supernus neither cross-examined on that opinion nor introduced any contrary evidence. Instead, it relied only on the other section—the working examples—to answer Actavis's written-description defense.

But the working examples did not support the claims, because (i) there was no showing that they were "homogeneous matrix" formulations, and (ii) nothing in the specification pointed to this alleged characteristic. The law of written-description does not permit an applicant to mine the specification for an undisclosed and undescribed characteristic of a working example and then broadly claim all formulations which share that characteristic. The district court erred in basing its conclusion on legally-irrelevant findings that (i) the specification

enabled making the claimed formulations, and (ii) an obvious goal of formulators (based on the prior art) would be to make their tablets homogeneous.

IV. The testimony of Supernus' infringement expert showed that "homogeneous matrix" is hopelessly indefinite because there was no standard either in the patent or the industry to determine if products satisfied this element. Asked on cross-examination to articulate the standard he applied to opine that the Actavis tablets infringed, his explanation boiled down to an arbitrary "I know it when I see it" approach. The district court erred in rejecting the indefiniteness defense based on its finding that formulators would know how to make their tablets homogeneous by reference to the specification's working examples, and could test them using FDA standards.

ARGUMENT

This Court reviews legal conclusions *de novo* and factual findings for clear error. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007).

Claim construction is a legal issue that is generally reviewed *de novo*, except findings of fact made by the district court that are necessary to construe the claims are reviewed for clear error. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1339 (Fed. Cir. 2015). Questions of indefiniteness are reviewed in a similar manner. *Id.* at 1341.

The question of whether the accused product or process is embraced by the properly construed claims is one of fact reviewed for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1361 (Fed. Cir. 2006).

Compliance with the written description requirement is a question of fact, and hence (absent an error of law) is reviewed under the clearly erroneous standard. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991).

A finding is clearly erroneous when "the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948).

I. Claim Construction Errors Require Reversal Of The Judgment Of Infringement Regarding "Homogeneous Matrix"

In its *Markman* decision, the district court construed "homogeneous matrix" as "a matrix in which the ingredients or constituents are uniformly dispersed." (Appx2744 ¶1). It did not elaborate on its reasoning at the time, but this construction was a rejection of that urged by Supernus, which was "a substantially uniform dispersion of one or more constituents in a given volume." (Appx21-22). As the district court later explained, it had rejected Supernus' construction because (i) it read "matrix" out of the claim, and (ii) the qualifier "substantially" had "no support in the intrinsic evidence." (Appx22).

Despite this, the district court erred by effectively abandoning the construction it adopted at the *Markman* stage in favor of a construction based on purported FDA standards that had no connection to the intrinsic evidence. Supernus led the district court into this error by improperly conflating "homogeneous matrix" in its patent claims with the standards used for FDA approval of commercial products, obtaining a construction that effectively was "anything that works unless it's a coated tablet." The legal error of this implicit construction falls into three broad categories.

First, it erroneously substitutes compliance with FDA regulatory standards for proof of infringement even though nothing in the intrinsic evidence points to FDA standards as defining elements of the claims.

Second, the regulatory standards that it adopted—blend uniformity, content uniformity, and dissolution testing—are not related to the claim element at issue (homogeneous matrix), which is directed to the spatial arrangement of ingredients within the matrix of each individual tablet. Rather, they are concerned only with making sure that each tablet has the correct amount of drug and releases that drug at the desired rate. Further, these tests are performed on tablets (or the intermediate blend) that has been completely dissolved, which negates any information on how the ingredients were physically distributed in the solid tablets.

Third, it broadened "homogenous matrix" by changing it from a recitation of what the product must be to an exclusion of what it must not be. Specifically, by adding the phrase "homogeneous matrix" to overcome an obviousness rejection, Supernus plainly gave up coverage of the prior-art formulation on which the rejection was based. (Appx14053; Appx14058-14061; Appx14086; Appx14089 ¶4). But it did not only give up that subject matter, as would have been the case if it had overcome the rejection with a negative limitation such as "provided that such formulation is not a coated tablet." Rather, it limited its claim scope to tablets in which the four recited ingredients are "a homogeneously admixed mixture" (to use the Examiner's words) or "uniformly dispersed" (to use the district court's original *Markman* construction). (Appx14072; Appx2744 ¶1).

These errors of construction (or reconstruction) expanded the scope of "homogenous matrix" beyond its permissible limits by adopting a construction that essentially is "anything that works except a coated tablet." Because the trial evidence excludes infringement under the correct construction, the judgment of infringement should be reversed, or at minimum vacated. *See Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1331 (2009) (district court's failure to follow its original claim construction required remand).

A. The District Court's *Markman* Decision Correctly Construed "Homogeneous Matrix" To Mean One In Which The Ingredients Are Uniformly Dispersed

At *Markman*, the district court properly afforded meaning to "homogeneous matrix" when it construed it as a matrix in which the ingredients are "uniformly dispersed." (Appx2744 ¶1). This was consistent with its ordinary meaning in view of the specification and prosecution history. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). In the chemical arts, "homogeneous" when applied to a mixture of ingredients is "used to describe a mixture or solution composed of two or more compounds or elements that are uniformly dispersed in each other." (Appx697-98).

During prosecution, "homogeneous matrix" was added to the claims to overcome prior art that included tablets in which the ingredients were divided between an inner core and outer coating. (Appx14053; Appx14058-14061;

Appx14089 ¶4). This means that "homogeneous matrix" necessarily excludes such formulations, but it does not mean it embraces everything but such formulations. *See Ecolab, Inc. v. Envirochem, Inc.*, 264 F.3d 1358, 1368 (Fed. Cir. 2001).

The "homogeneous matrix" claim element was added over the course of two amendments. The first added "matrix," (Appx14053; Appx14058-14061), butthe Examiner again rejected the claims because "matrix" did not limit the claims to "a homogeneously admixed mixture" of the four recited components. (Appx14072). In response, Supernus further amended the claims to read "homogeneous matrix." (Appx14086; Appx14089 ¶4).

Supernus could have tried for a less restrictive amendment that only excluded coated formulations (such as a negative limitation), and seen if the Examiner was satisfied that it was both (i) supported by the specification; and (ii) sufficient to overcome the obviousness rejection. But for better or worse, Supernus retreated to narrower claim language ("homogenous matrix"), perhaps because the Office Action suggested that the Examiner was looking for an amendment that limited the claims to a "homogenously admixed mixture." (Appx14072). Supernus could have resisted, and if the Examiner maintained the rejection, it could have appealed or continued prosecution. But having chosen to add a notably restrictive word ("homogeneous") to promptly gain allowance, Supernus cannot avoid the consequences of that choice by now obtaining a broader

claim on the theory that it did not need to add such a restrictive term. *See Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000).

B. The District Court Misconstrued Its Earlier Claim Construction To Read "Homogeneous Matrix" Out Of The Claims

A basic rule of construction is that elements should not be read out of the claims. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005). The error in this case is a bit different from most in which this error is seen, because it did not occur in the construction at the *Markman* stage. Rather, the district court subsequently "construed the construction" to an extent that nullified the *Markman* ruling and effectively read out the "matrix" limitation by analyzing the claim in terms of manufacturing methods and testing of tablets that are dissolved (liquid-state testing), with the result that the information present in the intact tablets (seen with the solid-state Raman testing) has been destroyed.

The issue here is not whether the district court acted within the latitude afforded it to resolve factual disputes. On most of what should have been the dispositive facts under the proper claim construction, there was no substantial disagreement. For example, Actavis relied on the Raman images made by Supernus' own expert, and there is no real dispute over the content of those images and what they show in regards to the distribution of ingredients within the Actavis tablet. Based on those images, Actavis was entitled to judgment of

noninfringement under the claim construction provided at the *Markman* stage without the need to resolve fact questions, because the two-step infringement analysis collapses to a single step (claim construction) when there is no material dispute concerning the characteristics of the accused product. *Gen. Mills, Inc. v. Hunt-Wesson, Inc.*, 103 F.3d 978, 983 (Fed. Cir. 1997).

Accordingly, the district court's treatment of the Raman images as essentially irrelevant to infringement (Appx46 n.15) is properly viewed as an error of claim construction, which determines what evidence is probative of infringement.

1. Homogeneous Matrix Does Not Mean "Substantially" Uniform

Despite reiterating its earlier *Markman* ruling, and again rejecting Supernus' proposed construction of "substantially" uniform, the district court *de facto* adopted and applied Supernus' erroneous construction. It acknowledged that Supernus' proposed construction was "problematic" because it "adds language to the claim—the word 'substantially'—that does not appear in the claim and has no support in the intrinsic evidence." (Appx22). It also correctly recognized that a "substantially" uniform claim construction would "write out the term 'matrix'" from the claims since there would no longer be "the requirement that the element be in the form of a matrix." (*Id*).

But the district court did an about face by ruling that a "substantially uniform" matrix is homogeneous, even though it recognized that such a construction had no support in the intrinsic record and read elements out of the claim. (Appx22; Appx59-60).

The district court paid particular attention to the definition of "homogeneous" in a chemical dictionary:

> **homogeneous.** (Latin, "the same kind"). This term, in its strict sense, describes the chemical constitution of a compound or element. A compound is homogeneous since it is composed of one and only one group of atoms represented by a formula. For example, pure water is homogeneous because it contains no other substance than is indicated by its formula, H_2O. Homogeneity is a characteristic property of compounds and elements (collectively called substances) as opposed to mixtures. The term is often loosely used to describe a mixture or solution composed of two or more compounds or elements that are uniformly dispersed in each other. Actually, no solution or mixture can be homogeneous; the situation is more accurately described by the phrase "uniformly dispersed." Thus so-called homogenized milk is not truly homogeneous; it is a mixture in which the fat particles have been mechanically reduced to a size that permits uniform dispersion and consequent stability.

(Appx697-98) (emphasis added). As is clear from that definition, when "homogeneous" is applied to a mixture of ingredients, it means "uniformly dispersed," even though in a strict sense, no mixture is homogeneous. While the court emphasized the "loosely" language to support its view that "homogenous" means a "substantially" uniform dispersion of ingredients (Appx24), the definition

uses "loosely" to contrast the strict definition with acceptable vernacular describing "uniformly dispersed" mixtures. (Appx697-98).

Thus, the dictionary definitions shows that when "homogeneous matrix" is used to describe a matrix of different ingredients, the ingredients must be uniformly dispersed, and not just "substantially" uniformly dispersed (whatever that means). (*Id.*; *see also* Appx693 ("uniform throughout in structure or makeup"); Appx702 ("[o]f uniform or similar nature throughout"); Appx706 ("having a uniform quality throughout")).

However, the court impermissibly relied on the opinion of Supernus' expert Dr. Little that a homogeneous matrix embraces substantial uniformity because one cannot achieve perfect homogeneity of mixtures. (Appx21-22 n.7; Appx25-27). Regardless of whether that is correct, it was legal error to rely on it to redefine "homogeneous" as "substantially uniform." *See Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 716-17 (Fed. Cir. 1998) (term's clear meaning "cannot be altered or superseded by witness testimony or other external sources simply because one of the parties wishes it were otherwise"); *Phillips*, 415 F.3d at 1318. Moreover, Dr. Little testified at *Markman* that there were processes by which one could achieve "complete uniformity" of a mixture. (Appx2389 73:12-19).

At minimum, the district court's reopening of *Markman* to re-construe "homogeneous matrix" caused substantial prejudice to Actavis requiring a new

trial. *See Ecolab Inc. v. Paraclipse, Inc.*, 285 F.3d 1362, 1376 (Fed. Cir. 2002) (noninfringement judgment vacated for new trial because erroneous claim construction caused sufficient prejudice). "Homogeneous matrix" was construed at *Markman* to mean a matrix in which all the ingredients are uniformly dispersed (Appx2744 ¶1), and Actavis went to trial in reliance on this construction. To be sure, a *Markman* ruling is interlocutory and may be reopened by the district court prior to final judgment. But at the same time, a litigant is permitted—indeed required on pain of sanctions—to abide by the *Markman* decision in presenting its evidence. *See MarcTec, LLC v. Johnson & Johnson*, 664 F.3d 907, 915-916 (Fed. Cir. 2012) (exceptional case award affirmed where party mischaracterized court's claim construction). Had Actavis been on notice that it was trying multiple cases on a range of possible constructions of "homogeneous matrix," including one where the matrix need only be "substantially" uniform, it would have presented more and different evidence on at least three points: first, to defend the original *Markman* ruling on which it had prevailed; second, to explore the fallacy of an infringement case that relied in large part on FDA standards that have nothing to do with patent infringement; and third, to present additional evidence of lack of written description and indefiniteness.

2. Homogeneous Matrix Does Not Mean Any Formulation Where the Ingredients are Not In The Coating Layer

By misinterpreting the prosecution history, the district court improperly broadened "homogeneous matrix" to mean "lacking a coating:"

> The term "homogeneous matrix" was added to the claims to distinguish Supernus' invention, which has all four matrix components in the tablet core, from the prior art references containing certain matrix constituents solely in the coating (which the Examiner had viewed to be part of the matrix). The term was not added to describe the degree of uniformity or homogeneity of the Supernus invention.

(Appx35) (emphasis added).

Supernus led the district court into error by arguing that "homogeneous matrix" means any mixture except one in which the ingredients are divided between a core and a coating.[3] This, of course, contradicts the ordinary meaning of "homogeneous matrix" and improperly relieves Supernus of the consequences of its decision during prosecution to obtain allowance by amending with notably restrictive language. *See Hockerson-Halberstadt*, 222 F.3d at 957. It also

[3] For example, in post-trial briefing, Supernus proposed the following finding of fact with respect to "homogeneous matrix," which the court adopted.

> 82. The term "homogeneous" was not added to the claims to distinguish the degree of uniformity of Supernus's claimed formulations from the degree of uniformity of prior-art formulations.

(Appx26192).

misinterprets the consequences of amendments, because even though the particular reference cited by the Examiner was a coated formulation, there is no basis for the proposition that the resulting amendment to add "homogeneous matrix" resulted in claims that embraced all other formulations (except the specific core/coating variety cited by the Examiner). There is no principled way under this (erroneous) approach to find that the Actavis formulation was a "homogeneous matrix" without also finding, for example, that a bilayer tablet is a "homogeneous matrix" because it too is different from the specific core/coating reference cited by the Examiner. But Supernus' infringement expert Dr. Bugay admitted that bilayer tablets were not within homogeneous matrix. (Appx12275-76 361:19-362:2).

3. Homogeneous Matrix Does Not Mean A Formulation Made By A Process Of Mixing

By relying upon Actavis' manufacturing process as proof of infringement of "homogeneous matrix," instead of the direct evidence showing the actual interior of Actavis' accused tablets, the court compounded the error of construction by elevating the way the product was made over the evidence of its structure and effectively converted composition claims into process claims. (Appx40; Appx46 n.15). For example, the court cited heavily to Dr. Little's testimony that because Actavis' manufacturing process includes steps of pre-mixing, granulation, milling, and final blending of the ingredients, which are all before the tablets are actually

formed, the finished tablet necessarily contains a "homogeneous matrix." (Appx37; Appx39).

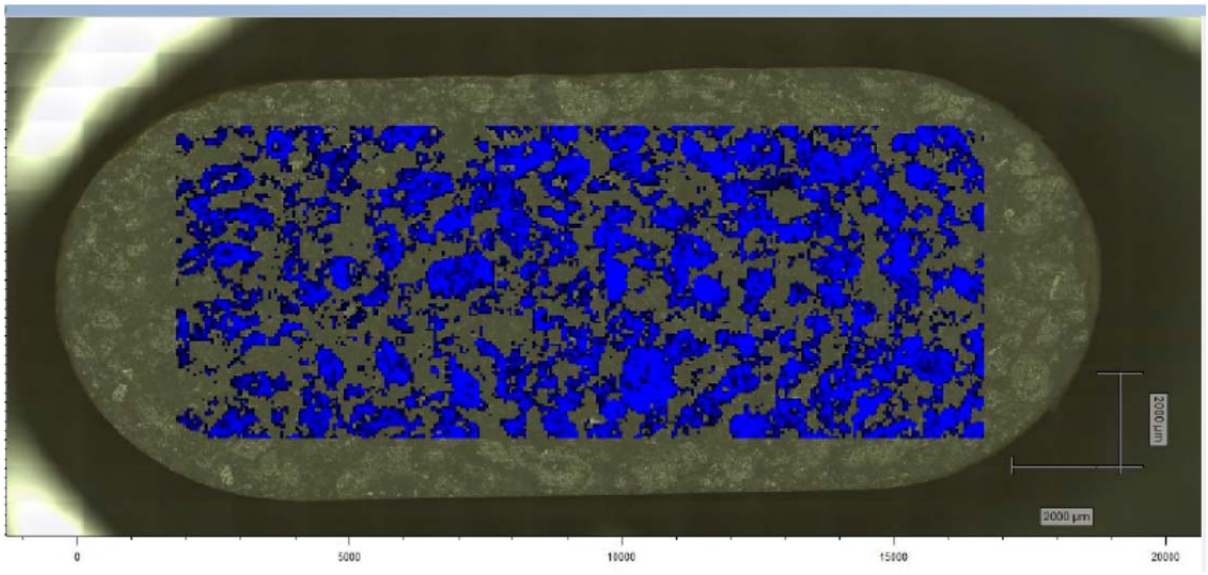
The proper construction of "homogeneous matrix" does not mean "made from the process of mixing and blending" or "made with conventional techniques." It is a term of structure of the finished tablet, not an element satisfied by a manufacturing process. *See Phillips*, 415 F.3d at 1311(structural term "baffles" is not "a general description of any structure that will perform a particular function"); *Ecolab*, 264 F.3d at 1367 ("substantially uniform" was structural term, not functional limitation). Because the court misconstrued "homogeneous matrix" as the result of conventional manufacturing processes, it erroneously elevated the method of manufacturing over direct evidence of structure. *Vanguard Products Corp. v. Parker Hannifin Corp*., 234 F.3d 1370, 1372 (Fed. Cir. 2000). Again relying upon the testimony of Supernus' experts, the court concluded that:

> Example 4 in the '898 patent sets forth a manufacturing process that involves blending and high shear granulation prior to tableting. '898 Patent, col. 10,11. 35-56. Actavis, too, utilizes blending and high shear granulation in the formulation of its ANDA tablets. [internal citations omitted] (Little Direct).
>
> The Court finds that Actavis's manufacturing process results in a homogeneous matrix in its tablets.

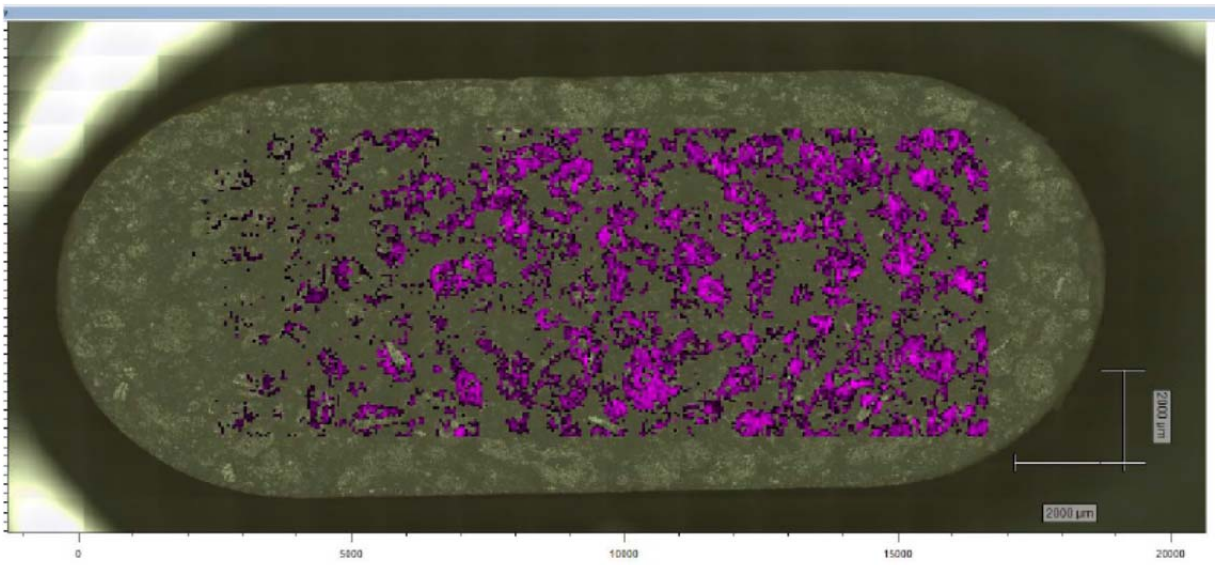
(Appx40).

C. There Is No Infringement Under The Correct Claim Construction Of "Homogeneous Matrix"

The district court's construction at the *Markman* stage required all ingredients to be uniformly dispersed within the matrix. (Appx2744 ¶1). Direct evidence of the arrangement of ingredients within Actavis' tablets was put in by both sides with no material dispute. (Appx23218-36; Appx25715-30; Appx25731-43 Appx25744-86). Indeed, Actavis relied largely on Supernus' evidence for its noninfringement case. (*See, e.g.*, Appx12810-817 896:6-902:20, 903:13-15). Chemical imaging of the interior of the accused tablets introduced by both sides showed that the ingredients are not uniformly dispersed within the formulation. For example, these are the chemical images by Supernus' expert Dr. Bugay, indicating the oxcarbazepine active ingredient in blue and the HPMC excipient in magenta within the accused tablets.



(Appx23219) (showing oxcarbazapine).

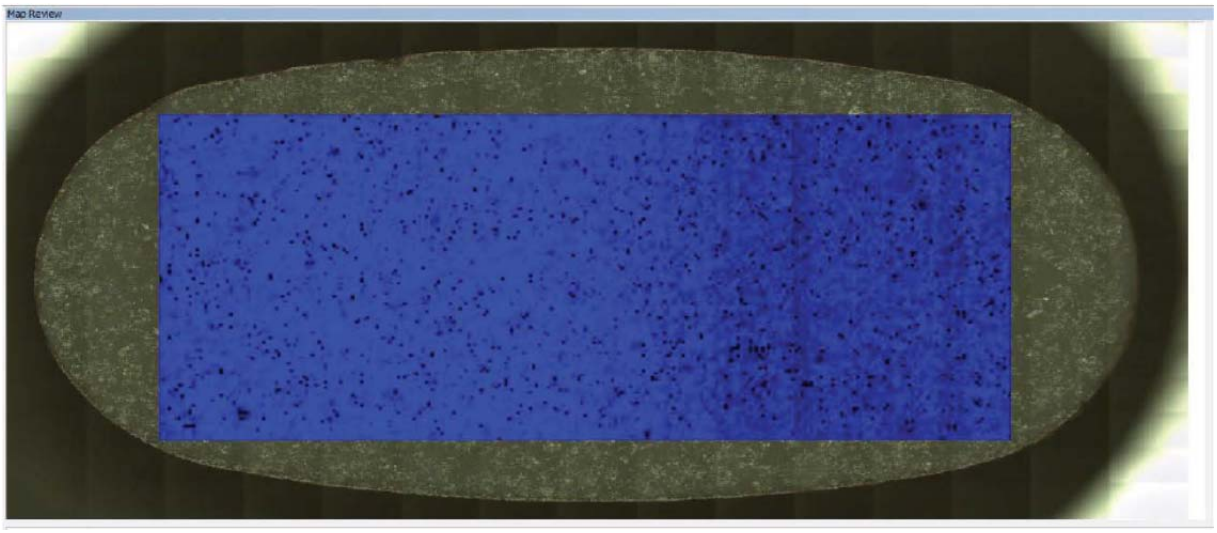


(Appx23225) (showing HPMC).

This reveals non-uniformity at two levels. First, there is significantly more oxcarbazepine and HPMC on the right side of the tablet. (Appx12814 900:1-25, referring to Appx23219: Appx12816 902:8-20, referring to Appx23225). Second, there is clear agglomeration of oxcarbazepine and HPMC, separated by areas where they are absent. (Appx12814 900:1-25, referring to Appx23219; Appx12816 902:8-20, referring to Appx23225; Appx12293-95 379:23-381:1 referring to Appx23232). Supernus' expert Dr. Bugay noted this agglomeration, as did Actavis' expert Dr. Muzzio. (*Id.*; Appx12810-11 896:6-897:19, referring to Appx23231; Appx12333 419:22-25). When there is agglomeration of ingredients, the literature describes the formulations as not uniform and not homogeneous. (Appx25920 ¶1, Appx25921 Fig.3A) (formulation "exhibits a great deal of heterogeneity with clearly defined domains of pure or nearly pure" active

ingredient.); (Appx25913 ¶3, Appx25914 Fig.7) ("it is possible to observe how MCC is forming some aggregates in not a very homogeneous distribution in several of the tablets analyzed (Fig. 7).").

Supernus responded by arguing that the chemical images of the Actavis tablets indicated that their ingredients were substantially uniformly dispersed, because actual uniformity in the form of monolithic tablet structures, *i.e.*, "to lay a brick wall and have the bricks end to end," was not possible. (Appx12255 341:5-23). To rebut this position, Actavis introduced chemical imaging of matrix formulations where the ingredients are actually uniformly dispersed, *i.e.*, a homogeneous matrix, such that there was an even distribution of ingredients without aggregation of materials. (Appx23241; Appx25880; Appx25920 ¶1, Appx25921 Fig.3B). This was seen in Supernus' chemical imaging of Oxtellar, as well as in the scientific literature.



(Appx23242) (oxcarbazepine in Oxtellar)

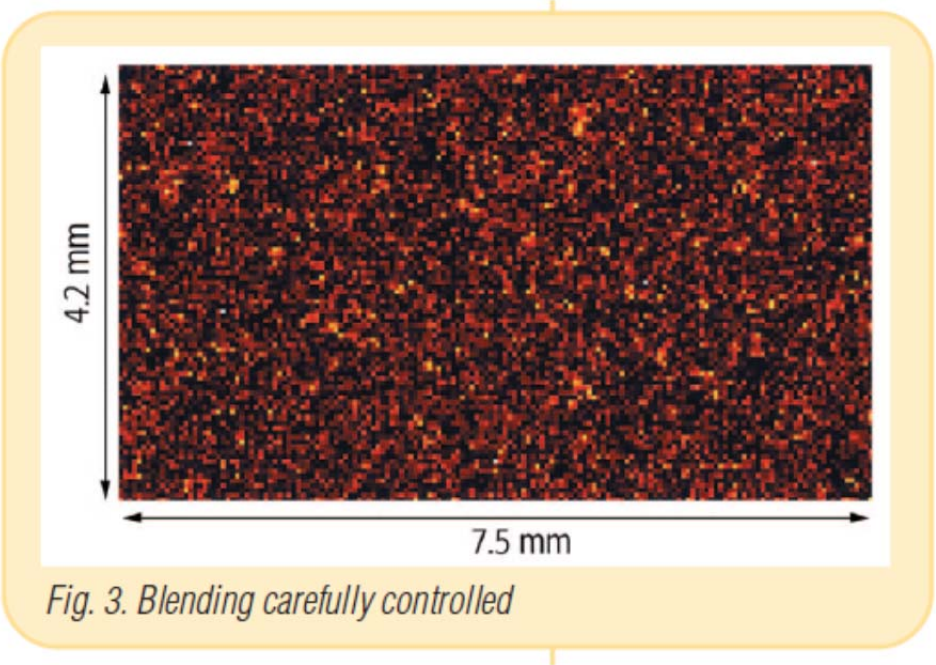
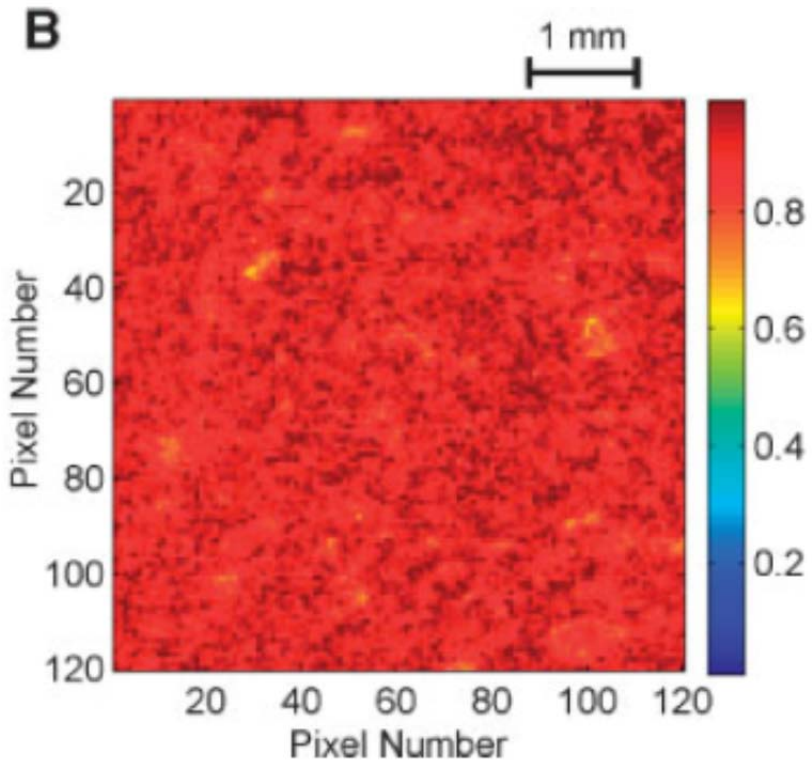


Fig. 3. Blending carefully controlled

(Appx25880 Figure 3)



(Appx25921, Figure 3B).

The district court erred by faulting Actavis for trying to limit the claims to the commercial embodiment by comparing its tablet to Oxtellar (Appx56-58), because Actavis did nothing of the sort. Rather, because Supernus was trying to broaden and redefine "homogeneous matrix" by arguing that homogeneity was unattainable, Actavis countered by showing what was indeed possible in a real-life commercial product (Oxtellar) that Supenus said was within its claims. (Appx12815 901:8-15; Appx12874 960:11-20; Appx25880; Appx25920 ¶1, Appx25921 Fig.3B).

Actavis also used the images of Oxtellar, and those of other homogeneous matrix formulations, to show how the claimed uniform dispersion of ingredients

could appear, since no description was provided in the patents. (*Id.*) In this way, these images are no less improper than the opinions of Supernus' experts when they testified that the chemical images of the interior of Actavis's tablets looked like a homogeneous matrix (Appx12233-34 319:24-320:7; Appx12255 341:5-13; Appx12256-57 342:17-343:12; Appx12551-53 637:24-639:17) even though, objectively, the chemical images clearly showed that the ingredients were agglomerated and shifted to one side. (Appx12810-11 896:6-897:19, referring to Appx23231; 900:1-25, referring to Appx23219; Appx12816 902:8-20, referring to Appx23225; Appx12293-95 379:23-381:1, referring to Appx23232; Appx12333 419:22-25; Appx12814 900:1-25, referring to Appx23219; Appx12816 902:8-20, referring to Appx23225). Surely, Actavis had the right to present contrary evidence (rather than just the opinions of experts) showing that a uniform dispersion of ingredients looks nothing like the chemical images of the Actavis tablets because chemical images of actual uniformity can be shown in the literature as well as from Supernus' own tests of its Oxtellar product.[4]

The court also inferred infringement based on statements made in Actavis' manufacturing documents stating that the accused product passed FDA tests of blend and content uniformity. (Appx42; Appx44; Appx46). However, nothing in

[4] Supernus obtained Raman imaging of Oxtellar to argue it was an embodiment of the asserted claims for commercial success. (Appx12232-33 318:24-319:5; Appx125-28).

the intrinsic evidence equates "homogeneous matrix" to following good manufacturing practices or complying with regulatory standards.

The fact that Actavis' in-process blend (which is not tablets) satisfies regulatory standards for blend uniformity is not tantamount to the finished tablets having the claimed homogeneous matrix. (Appx12849-51 935:17-937:1). Blend uniformity tests only the amount of active ingredient in the blend. (Appx25119 ll.88-89). By contrast, the claimed "homogeneous matrix" must be found in the tablets. (Appx12805-06 891:22-892:16). The "uniformity" in the term "blend uniformity" refers to whether there is the same amount of active ingredient from samples taken from different areas of the vessel holding the blend, not how the ingredients are dispersed in finished tablets. (Appx12850-51 936:6-937:1). Moreover, blend uniformity measures only the amount of drug, not the excipients. (Appx25119 ll.93-95).

Similarly, that Actavis' tablets pass content uniformity does not does not mean they comprise a homogeneous matrix. (Appx12854-55 940:23-941:7; Appx25119 ll.88-95). Content uniformity tests the amount of drug in a group of tablets, not the spatial distribution of drug within the matrix of a tablet. (Appx12856 942:3-22). As with blend uniformity, it does not test for excipients, and "uniformity" requires only the same amount of drug in each tablet, not whether all ingredients are uniformly dispersed within a tablet. (*Id*.) Content uniformity

does not measure the spatial distribution of the ingredients in the solid tablets, because they are destroyed, then dissolved in liquid to be when assayed. (Appx12629-30 715:21-716:5). Because these tests are performed on dissolved tablets, they cannot measure the spatial distribution of ingredients within intact tablets.

Thus, the court clearly erred when it inferred infringement from compliance with regulatory standards in the face of direct evidence (the Raman imaging) that the ingredients in the Actavis tablets were not uniformly dispersed. *See Takeda Pharm. Co. v. Teva Pharms. USA, Inc.*, 542 F. Supp. 2d 342 (D. Del.) (finding no infringement because "overall content of each drug capsule, however, does not bear on the question of whether the distribution of lansoprazole [drug] and magnesium carbonate [salt] is 'even' as the claims require"), *aff'd*, 298 Fed. Appx. 969 (Fed. Cir. 2008).

Finally, the district court erred when it inferred infringement because "the default objective" of formulators "would be to create a homogeneous matrix formulation." (Appx35-36). First, to the extent Actavis' expert Dr. Hopfenberg testified that a homogeneous matrix was a default objective, it was within the context of his obviousness opinion that this element "would be an obvious objective of the skilled formulator." (Appx13406 1493:3-17). Here, where Supernus never asserted infringement under the doctrine of equivalents, there can

be no question that the obviousness of "homogeneous matrix" cannot satisfy the infringement of this element in Actavis' tablets. *See Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1282 (Fed. Cir. 2011). Just because a "homogeneous matrix" is obvious does not mean it necessarily occurs.

Second, even assuming for argument's sake that it was the default objective, the evidence at trial demonstrated that Actavis departed substantially from the manufacturing process described in the patents. While the patents use a large amount of the SLS solubility enhancer (Appx240 11:15-30), which is known to promote uniform granulation (Appx12843 929:16-23), Actavis does not use SLS or any solubility enhancer (*Id.*; Appx21623 Table 1). Moreover, Actavis' process creates relatively large granules in the range of several hundred microns. (Appx12843-44 929:24-930:9). Actavis then adds a significant amount of extragranular material. (*Id.*) This includes a double-digit percentage of microcrystalline cellulose (Appx21623 Table 1; Appx12844-45 930:23-931:6), in contrast to the very small amount of extragranular material (0.5% of magnesium stearate) described in the patents (Appx239 10:52-54). As explained by Dr. Muzzio at trial, Actavis improved compactibility (hardness) of its tablets by keeping the MCC outside the granules. (Appx12845 931:9-23).

The district court's observation that parts of the specification contemplate adding extragranular materials (Appx39) does not support an infringement finding. There are many disclosures in the patent, and no basis to conclude they are all embraced by the claims. For example, the patents also contemplate "multi-layer tablets," which Supernus admitted cannot comprise a homogeneous matrix. (Appx237 6:39-48; Appx12275-76 361:19-362:2; Appx12635 721:15-20).

II. The District Court Erred In Finding That The Actavis Tablets Comprise A Solubility Enhancing Agent

Supernus' inventions are directed to enhanced formulations of oxcarbazepine that can be administered once-a-day because, among other things, they contain a solubility enhancing agent. The story of their development, laid out in the patents and trial testimony, prove that PVP-K90 is not a solubility enhancer as claimed. It was only by committing legal error in not applying the ordinary meaning of "agent that enhances the solubility of oxcarbazepine" that the district court could make this erroneous infringement finding.

Supernus' development of extended-release oxcarbazepine began under contract with Jazz Pharmaceuticals. (Appx11963-64 49:22-50:22).[5] Three early formulations said by the specification and inventors to lack a solubility enhancer are reported in Example 1 of the patent. (Appx239 9:10-37; Appx235 2:60-62;

[5] At the time, Supernus was called Shire Laboratories. (Appx11960 46:10-14).

agent is not a solubility enhancer. (Appx239 9:10-37).

TABLE 1

Formula composition of Oxcarbazepine CR formulations with changing slope

Ingredients	SLI 530 CR-F (Fast)	SLI530 CR-M (Medium)	SLI530 CR-S (Slow)
Oxcarbazepine	60	60	60
Compritol 888ATO	9.5	7	—
Prosolv HD90	9.8	20.3	15
Kollidon 25	10	—	—
Kollidon 90	—	3	—
Methocel E5 Prem. LV	—	—	10
Methocel K4M Premium CR	—	—	5
Carbopol 971P	10	9	9
Mg Stearate	0.5	0.5	0.5
FD&C Red #40	—	—	0.5
FD&C Blue #1	0.2	—	—
FD&C Yellow #6	—	0.2	—
Anhydrous Ethanol	*	*	*
Total	100	100	100

*Removed during processing

(*Id*.) These non-enhanced formulations were compared to Trileptal, to determine their pharmacokinetics. (Appx239 9:38-67). This is shown in Example 2. (*Id*.)

TABLE 2

Pharmacokinetic parameters of the three exemplary formulations in example 1 and immediate release reference product.

PK Parameters	CR-F Fast	CR-M Med	CR-S Slow	Trileptal ™ IR
T_{max} (Hr)	6.5	8.4	9.1	1.4
C_{max} (ug/mL)	0.248	0.146	0.103	1.412
AUC_{last} (Hr * ug/mL)	3.0	2.5	1.7	5.7
Rel BA	53%	44%	30%	100%

(*Id*.) When the inventors reviewed this data, they concluded that these non-enhanced formulations were failures. (Appx11981 67:11-17; Appx23135 ¶1; Appx12025 111:15-20). The patents make clear that these non-enhanced formulations, one of which contains PVP-K90, lack a solubility enhancer. For example, the patent states that "FIG. 1 shows the dissolution profiles for the three exemplary (CR-F, CR-M, and CR-S) oxcarbazepine formulations containing no solubility/release enhancer." (Appx235 2:60-62). And Dr. Bhatt confirmed at trial that these non-enhanced formulations—one of which included PVP-K90—did not contain a solubility enhancer. (Appx12038 125:1-11; Appx12023 111:10-14).

Dr. Bhatt thus decided to add a solubility enhancer to the failed prototypes. (Appx12025 111:7-20). The inventors thus screened different excipients as possible solubility enhancers, as reported in Example 3. (Appx239 10:1-31; Appx12030 116:12-15; Appx12031-34 117:19-120:13). They settled on sodium lauryl sulfate ("SLS"), and made what the patent calls the "enhanced" formulations of Example 4. (Appx239-40 10:55-11:15; Appx12031-34 117:19-120:13).

Even the FDA was of the view that the Actavis tablets lacked a solubility enhancer, because it wrote to Actavis asking whether the absence of a solubility enhancer would have any effect on the product's performance. (Appx21679 ¶5).

A. The Ordinary Meaning Of The Term "Agent That Enhances The Solubility Of Oxcarbazepine" Requires That It Actually Enhances Oxcarbazepine Solubility In The Pharmaceutical Formulation

At *Markman*, the district court held that "agent that enhances the solubility of oxcarbazepine" required no construction because its ordinary meaning should apply. (Appx2481). That ordinary meaning clearly indicates that this agent must enhance the solubility of oxcarbazepine in the claimed formulation.

There really is no dispute here regarding its ordinary meaning. At *Markman*, Supernus emphasized on direct examination of its expert Dr. Little that the solubilizer must function in the claimed pharmaceutical formulation.

> So it seems like [defendants' construction] perhaps is out of context or could it be done perhaps where the solubility is enhanced the (sic) someplace else but not necessarily in the formulation itself. So, my construction says "the oxcarbazepine" which I'm implying that that's the oxcarbazepine <u>in the formulation</u>.

(Appx2401 85:18-23) (emphasis added).

The preamble of claim 1, which contains the structural "homogeneous matrix" element, designates that the solubilizing agent is comprised in the finished formulation:

> A pharmaceutical formulation for once-a-day administration of oxcarbazepine comprising a homogeneous matrix comprising:
>
> . . .

> (c) at least one agent that enhances the solubility of oxcarbazepine…

(Appx240 12:52-63). This is also confirmed by the specification, which states that the "object of the invention [is] to incorporate a combination of solubility-enhancing excipients and/or release-promoting agents into the formulations to enhance the bioavailability of oxcarbazepine. . . ." (Appx236 3:56-60).

Thus, in order for the district court to have concluded that the Actavis tablets met this element, the evidence had to demonstrate that the Actavis tablets contained an agent that functions to enhance the solubility of oxcarbazepine in the Actavis tablets.

B. The Patents, The Inventor Statements, And Statements By The FDA Consistently Show That PVP-K90 Is Not An "Agent That Enhances The Solubility Of Oxcarbazepine"

1. The Specification Shows That PVP Does Not Enhance The Solubility Of Oxcarbazepine

The patents rule out that PVP, and specifically PVP-K90, is an agent that enhances the solubility of oxcarbazepine in the formulation.

In describing the formulations of Table 4 of Example 4, the patent specification states that "FIG. 5 shows the dissolution profiles of oxcarbazepine CR formulations with solubility enhancer (CRe), [and] without solubility enhancer (CR) . . . ." (Appx236 3:14-19). Yet both the "enhanced" and "non-enhanced" formulations of Table 4 contain PVP. (Appx239-40 10:55-11:15). Thus, the PVP

in the non-enhanced formulation (CR), described as "without solubility enhancer," cannot be an "agent that enhances the solubility of oxcarbazepine."

In describing the three non-enhanced oxcarbazepine formulations (one of which contains PVP-K90) of Example 1, Table 1, the patent specification states that "FIG. 1 shows the dissolution profiles for the three exemplary (CR-F, CR-M, and CR-S) oxcarbazepine formulations containing no solubility/release enhancer." (Appx235 2:60-62) (emphasis added); (Appx239 9:10-37).

The named inventor, Dr. Bhatt, confirmed this when he testified that none of these three non-enhanced formulations (again, one of which contained PVP-K90), had a solubility enhancer.

> Q. Okay. So, if we can look, for example, in the patent at column 9, table 1, we see three formulations -- maybe we can blow that up -- that are called SLI530 CR-F, CR-M and CR-S.
>
> Are you with me, Doctor?
>
> A. Yes.
>
> . . .
>
> Q. These are formulations you made for Jazz, right?
>
> A. Yes.
>
> Q. Without a solubility enhancer, right?
>
> A. That's correct.

(Appx12039 125:1-11). Because none of these formulations had a solubility enhancer, Dr. Bhatt testified that he needed to add one to achieve his goal of a once-a-day oxcarbazepine formulation.

> Q. Okay. Now, you suggested to Jazz that after the pharmacokinetic results came in from your three non-enhanced prototypes to investigate using a solubility enhancer, correct?
>
> A. I did.

(Appx12025 111:10-14).

Consistent with the patent and Dr. Bhatt's testimony, the inventors' internal documents also show that PVP-K90 is not a solubility enhancer. A report authored by coinventor Dr. Kidane and approved by Dr. Bhatt characterized PVP-K90 as a strong binder "which lacks the solubilizing capacity" of a lower molecular-weight PVP:

> The incorporation of Povidone K90, a high molecular weight polyvinyl pyrrolidone, resulted in slow release profiles. Povidone K90 is a strong binder. It also lacks the solubilizing capacity of Povidone K25 resulting in slow release profiles.

(Appx25851) (emphasis added).

2. The Specification Teaches That Higher Molecular Weight Grades Of PVP, Such As PVP-K90, Do Not Enhance Oxcarbazepine Solubility

The undisputed evidence at trial proved that PVP-K90, the PVP in the Actavis tablets (Appx22940), with an approximate molecular weight of 1,000,000

(Appx25822 Table 1), is not a low molecular weight PVP. The inventors characterized PVP-K90 as "a high molecular weight polyvinyl pyrrolidone." (Appx25851). Supernus' expert Dr. Little agreed that he would not characterize PVP-K90 as low molecular weight. (Appx12603 689:3-17).

Yet, the specification only identifies that low molecular weight PVP is a solubility enhancer. (Appx237 5:14-15). By contrast, when the specification calls out a different use for PVP as the matrix forming polymer, it is not described as "low molecular weight." (Appx237 6:7-21; Appx240 12:56-59; Appx241 14:34-39).

In addition, PVP of considerably lower molecular weight than PVP-K90 does not enhance the solubility of oxcarbazepine.[6] Example 3 demonstrates that PVP-K17 (approximate molecular weight of 10,000) actually decreases the solubility of oxcarbazepine (Appx239 10:1-31; Appx25822, Table 1); oxcarbazepine solubility is markedly lower in a 1% PVP-K17 solution than in the control. (*Id*.; Appx13289 1376:7-20). Table 4 of Example 4 shows that PVP-K25 (approximate molecular weight 30,000) is not a solubility enhancer. (Appx239-40 10:55-11:15; Appx25822, Table 1). Table 4 provides the composition of an "enhanced" and a "non-enhanced" pharmaceutical formulation of oxcarbazepine, both of which contain 5% PVP-K25. (Appx239-40 10:55-11:15). Yet, the

[6] The district court found that "the molecular weight does not impact the ability of [PVP] to create a complex" to enhance the solubility of oxcarbazepine. (Appx64).

specification describes the non-enhanced formulation as "without solubility enhancer" and the enhanced formulation as "with solubility enhancer." (Appx236 3:14-19).

3. The FDA Stated That The Actavis Tablets Lacked A Solubility Enhancing Agent

Even the FDA recognized that the PVP-K90 in Actavis' tablet is not an agent that enhances the solubility of oxcarbazepine in the formulation, asking Actavis to address the fact that "[t]here is no solubility enhancing agent in the generic formulation." (Appx21679 ¶5).

Supernus led the district court to believe that Actavis responded to the FDA by saying that PVP-K90 was the solubility enhancing agent because it was being used as a wetting agent. (Appx65-67). But this was clearly not the case. Actavis' actual response on this issue is excerpted below:

> Oxcarbazepine is formulated with an aqueous wet granulation process using a water soluble binder. This granulation process increased the wettability of Oxcarbazepine by reducing the contact angle. For low solubility drugs like Oxcarbazepine, the principal mechanism of drug release is erosion of the matrix (disentanglement of hydrated matrix chains from the matrix surface, carrying the undissolved drug in the surrounding dissolution medium).

(Appx21473-74 ¶5 Response). Thus, Actavis explained that it did not need a solubility enhancing agent because the "principal mechanism of drug release [in its

formulation] is erosion," which carries "the undissolved drug" in the surrounding medium. (*Id*. (emphasis added)).

Even if PVP-K90 were a wetting agent, that does not mean it is an agent that enhances the solubility of oxcarbazepine. Dr. Hopfenberg explained that a wetting agent increases the ability of a liquid to spread over a solid surface in the presence of air—like a bead of water spreading on glass. (Appx13383 1470:5-11; Appx13383-84 1470:24-1471:8). However, the spreading of a liquid over the solid surface does not necessarily increase the solubility of that solid. Dr. Hopfenberg testified that a wetting agent is one type of surface active agent (Appx13388-89 1475:14-1476:4), not all surface active agents enhance the solubility of oxcarbazepine (Appx11985-86 71:25-72:3; Appx12033 119:2-7 (Bhatt)).

C. None Of The Evidence Submitted By Supernus Showed That The Amount Of PVP-K90 In Actavis' Tablets Solubilizes Oxcarbazepine In The Actual Formulation

The claimed "agent that enhances the solubility of oxcarbazepine" requires the agent to actually enhance the solubility in the claimed pharmaceutical formulation. Supernus presented no evidence showing that the trace amount of PVP-K90 in the Actavis tablets does this. (Appx22940). In fact, the Raman images made by Supernus of the Actavis tablet could not even detect the PVP-K90 because of its trace amount. (Appx12272 358:11-15; Appx12273-74 359:21-360:3).

Supernus' evidence at trial regarding this element can be broken down into two categories: (i) the Chyall data; and (ii) industry papers. Because none of this evidence proved that the PVP-K90 in the Actavis tablets solubilizes oxcarbazepine within those tablets, there can be no infringement. *See Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1340-41 (Fed. Cir. 2013) (affirming judgment of noninfringement where tests conducted in water were insufficient to show the behavior of ingredients in saliva); *Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1319-20 (Fed. Cir. 2006) (affirming judgment of noninfringement where no tests of the actual accused products were performed).

1. The Chyall Data

The district court relied heavily on the testimony of Drs. Chyall and Little regarding Dr. Chyall's testing of the solubility of oxcarbazepine in solutions of PVP-K90. (Appx62-63). Those tests, however, did not address any effect of PVP-K90 on the solubility of oxcarbazepine <u>in the Actavis tablets.</u> This was noted by the district court (Appx62), by Dr. Chyall on cross-examination (Appx12111 297:1-8), and by Dr. Hopfenberg (Appx13276 1363:16-18).

It is undisputed that there is less than 0.5% PVP-K90 in the Actavis tablets. (Appx22940). However, none of Dr. Chyall's tests evaluated oxcarbazepine solubility at this trace amount. (Appx12200-01 286:15-287:2;). Dr. Chyall tested the ability of 1%, 5% and 10% PVP-K90 to solubilize oxcarbazepine, but he did

not expressly say that 1% PVP-K90 enhanced solubility, nor did he rule out the possibility that the very small difference between 1% PVP-K90 and the control was within experimental error, which he did not determine. (Appx12200-01 286:15-287:2; Appx12206-07 292:16-293:22; Appx12213 299:6-19).

This was fatal to Supernus' infringement case to this element, as recognized by Dr. Little at *Markman*. There, he testified that if the accused solubilizer were only present in an amount insufficient to enhance the solubility of oxcarbazepine, it would not satisfy the claim element.

> Q. So I think what you are suggesting is that what we require here is a functional quantity of an agent that enhances the solubility of oxcarbazepine?
>
> A. I mean, it -- you are adding it to increase the solubility, so if you add it in some miniscule amount and it doesn't enhance the solubility, then that's not what we're talking about here.

(Appx2413-14 97:25-98:6).

The district court erroneously relied on Dr. Little's opinion that Dr. Chyall's "test tube test" led him to "expect in the actual tablet itself that [PVP-K90] would enhance the solubility of oxcarbazepine." (Appx12565 651:2-20; *see* Appx60 citing Tr. 651:2-20 (Little Direct)). But Dr. Little's reasoning is in conflict with the actual evidence because Dr. Chyall's "test tube test" did not show that the low amount of PVP-K90 in the Actavis tablets would enhance the solubility of oxcarbazepine. In fact, the PVP-K90 in Actavis' tablets was so low as to be

undetectable by Dr. Bugay's Raman spectroscopy (Appx12272 358:11-15), and, contrary to Dr. Little's expectation (Appx12565 651:12-20), was not shown to be co-located with oxcarbazepine. Dr. Bugay testified:

> Q. And you testified that you weren't able to actually create a Raman image of Povidone because the levels of detection on your instruments did not allow it to be detected, correct?
>
> A. I'll clarify that. For the Actavis product.

(Appx12272 358:11-15),

> Q. And just to be clear, in the Actavis tablet that you tested, you weren't able to create any image for the Povidone, correct?
>
> A. I tried to create an image for the Povidone, and, unfortunately, with respect to the slice that we were working at, I did not see any. So, either the Povidone was at too low of a concentration on that slice or nonexistent on that slice, as her Honor mentioned.

(Appx12273-74 359:21-360:3).

Nor did Dr. Chyall account for the effects of the other excipients in the Actavis tablets on the solubility of oxcarbazepine or on the ability of PVP-K90 to enhance the solubility of oxcarbazepine. (Appx12198 284:17-22; Appx12201-02 286:15-287:19; Appx12211 297:1-8). Table 3 of the specification of the patents-in-suit demonstrates that the ability of an excipient to solubilize oxcarbazepine can be affected by other excipients. (Appx239 10:15-31). For example, although hydroxypropyl betacyclodextrin ("HBCD") and sodium lauryl sulfate ("SLS")

each increased the solubility of oxcarbazepine in solution when tested individually, the combination of these two excipients actually reduced the solubility of oxcarbazepine as compared to the phosphate buffer control. (Appx239 10:15-31; *see also* Appx13284-88 1371:9-1375:13). Dr. Hopfenberg explained that because of this "you'd have to understand what the solubility is in the presence of every other component involved in the tablet. And simply measuring a single possible solubilizer by itself doesn't tell the whole story. It can actually give a distorted story." (Appx13288 1375:18-25).[7]

2. Industry Papers

The sales brochures and handbook relied on by Supernus did not address the ability of PVP-K90 to solubilize oxcarbazepine, let alone to do so in a formulation like the Actavis tablets. They stated only that PVP can be used to improve the bioavailability and increase the solubility of poorly soluble drugs as a general approach, without mentioning oxcarbazepine by name. (Appx12564 650:5-20; Appx12565-67 651:21-653:3).

But Dr. Bhatt testified that, just because an agent solubilizes one drug compound, it does not mean it will do so for oxcarbazepine:

> Every drug molecule is unique in its own right. Just because we have used component A in a previous drug

[7] Dr. Chyall also failed to explain why his control solubility for oxcarbazepine in buffer (0.0626 mg/mL) was not even close to that reported in the patents (0.4009 mg/mL). (Appx12206 292:16-19; Appx239 10:15-31, Table 3).

> product does not guarantee that that component is going to be acceptable in a project that is using drug B. Oxcarbazepine is a – is a chemical with its own properties. It has its own physical properties, and it behooves us as good scientists to study even standard excipients to ensure that those standard, quote/unquote, standard excipients are going to be compatible with the drug at hand, which is oxcarbazepine.

(Appx11985-86 71:25-72:3). Dr. Bhatt further explained that "there is no one ingredient that enhances solubility of every drug." (Appx12033 119:2-7). Thus, evidence referring to the general ability of PVP or PVP-K90 to solubilize some drugs, does not prove that PVP-K90 enhances the solubility of oxcarbazepine under any conditions, and certainly not in the Actavis tablets.

D. The District Court's Findings Were Clearly Erroneous Requiring Reversal Or Remand

A patent specification's teaching that a specific ingredient is not within an element of the claims—here the disclosure that PVP-K90 is not a solubility enhancer as claimed—can negate infringement if the patentee later alleges to the contrary. *See In re Omeprazole Patent Litig.*, 490 F. Supp. 2d 381, 430 (S.D.N.Y. 2007), *aff'd* 281 Fed. App'x 974 (Fed. Cir. 2008). There, the patentee argued that the talc in the accused product met the claimed requirement for an alkaline reacting compound ("ARC"). *Id.* The court disagreed, noting that "talc is not included in the patents' list of potential ARCs." *Id.* In addition, the court noted that the patent specifications "explicitly mention talc as an 'ordinary additive' to be used in the

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separating layer, in addition to an ARC, and as a dispersant to be added into the enteric coating." *Id.* Based on the disclosure of a different function and purpose for talc, the court concluded that "[t]he patent teaches by implication that talc is not an ARC." *Id*.

Applied here, the "non-enhanced" formulation is described as "without solubility enhancer," while the "enhanced" formulation containing SLS—a compound identified as a solubility enhancing agent [redacted] (Appx13548-49 1635:21-1636:19)—is characterized as "with solubility enhancer," even though both formulations have PVP. (Appx236 3:14-19), and Dr. Bhatt testified that formulations containing PVP lacked a solubility enhancer. (Appx12039 125:1-11; Appx 12025 111:10-14). Thus, the patents show that PVP-K90 (the specific grade in the Actavis tablet), is not an agent that enhances the solubility of oxcarbazepine in the accused Actavis tablets.

Moreover, the specification lists only "low molecular weight" PVP as a solubilizing agent (Appx237 5:14-16) and demonstrates that grades of PVP with molecular weights of 10,000 and above do not solubilize oxcarbazepine (*vide supra* II.B.2). Thus, the high molecular weight PVP-K90 in the Actavis tablets is not an "agent that enhances the solubility of oxcarbazepine." Like *Omeprazole*, which found that talc did not meet the claim requirement for ARC because, *inter alia*, the patents mentioned talc as an "ordinary additive" or a "dispersant" to be

used "*in addition to an ARC,*" 490 F. Supp. 2d at 430, the patents here identify PVPs that are not of low molecular weight, such as the PVP-K90 in the Actavis tables, as a matrix-forming polymer to be used in addition to an agent that solubilizes oxcarbazepine. (Appx237 6:7-21; Appx240 12:55-60; Appx241 14:34-40).

III. The Asserted Claims Are Invalid For Lack Of Written Description Because The As-Filed Application Did Not Describe "Homogeneous Matrix" Formulations As Ultimately Claimed

As noted previously, the "homogeneous matrix" element was added in two steps during prosecution to overcome an obviousness rejection, first by an amendment that added "matrix" and second by one that added "homogenous." (Appx14053; Appx14058-14061; Appx14089 ¶4). For support of the ultimate amendment, Supernus cited two sections of the specification. (Appx14089 ¶4).

First, Supernus directed the Examiner to the following passage that used the phrase "homogeneous matrix" to describe how the matrix-forming polymer swells and hydrates after the formulation is ingested:

> The desired drug release pattern contemplated by this invention is achieved by using "matrix" polymers that hydrate and swell in aqueous media, such as biological fluids. <u>As these polymers swell, they form a homogenous matrix structure that maintains its shape during drug release and serves as a carrier</u> for the drug, solubility enhancers and/or release promoters. The initial matrix polymer hydration phase results in slow-release of the drug (lag phase). Once the polymer is fully hydrated and swollen, the porosity of the matrix increases due to

> the leaching out of the pH-dependent release promoters, and drug is released at a faster rate. The rate of the drug release then becomes constant, and is a function of drug diffusion through the hydrated polymer gel.

(Appx596 5:53-65) (emphasis added); (Appx14089 ¶4) (pointing to as-filed paragraph 34 of the application).

Second, Supernus alleged that "homogeneous matrix" was supported by the examples generally, not pointing to a specific one, but writing that:

> As well, one of ordinary skill in the art would appreciate the fact that the formulations derived according to the protocol set forth in the Examples would necessarily comprise a homogeneous matrix.

(Appx14089 ¶4).

At trial, however, Supernus relied only on this latter disclosure (the examples) in response to Actavis's written-description defense.[8] Presumably, that is because it had no answer to Dr. Hopfenberg's testimony that the usage of "homogenous matrix" in the portion of the specification block-quoted above (paragraph 34 of the application) was completely different from its usage in the

[8] For example, in its opening post-trial brief, Supernus argued only that "homogenous matrix" was adequately described because of Example 4 and that the inventors stated during prosecution that "[o]ne of ordinary skill in the art would appreciate that the formulations derived according to the protocol set forth in the Examples would necessarily comprise a homogeneous matrix." [internal citation omitted]. (Appx26171). In fact, in its responsive post-trial brief, Supernus argued that the polymer swelling statements in the patent cannot support written description because it contradicts the court's claim construction. (Appx26511).

claims, and made no effort to rebut that testimony either by cross-examination or through its own witnesses. Specifically, he explained that "homogenous matrix" in the specification described only the matrix-forming polymer once it was hydrated to the point of equilibrium, and not the mixture of all four components in a "homogeneous matrix" as ultimately claimed (Appx13299-13302 1386:2-1389:16):

> The homogeneous matrix that's described is a matrix that only has two components, it has the matrix polymer and the matrix polymer has now been swollen. Call hydration and swelling. Hydration means the stuff that swelled it was water. It's hydrated. What do we have in that polymer now? We have only the polymer that we started with plus water. Nothing else. The homogeneous matrix has two components. What does it do? What does it serve as in this formulation? That disclosure tells us. It serves as a carrier for separate components that are not within the scope of it. It does something. It being the homogeneous matrix. It carries the drug, it carries the solubilizer, it carries the release promoter. Those other compounds are external to the matrix. The matrix is a separate entity.
>
> …Your Honor, if we look at Claim 1, we see that "homogeneous matrix" is set forth very clearly. "Homogeneous matrix" comprises within its scope not only the matrix polymer, which is element (b), but also has within its scope the drug oxcarbazepine. Also has within its scope the solubility enhancer. Also has with its scope, as claimed, the release promoter. There is a complete disconnect between what is described in that specification and what is claimed.

(Appx13301-13302 1388:1-1389:12).

What remains by way of alleged support, the working examples, are insufficient as a matter of law to support the claims because they do not remotely disclose the breadth of the claims. First, only Example 4 discloses a formulation containing all of the four ingredients ultimately required by the claims. (Appx239-40 10:33-11:30). And even that discloses only three formulations (Table 5) that have all four ingredients.[9] (*Id*.)

Second, nothing in the specification discloses that the "enhanced" formulations (with all four ingredients) in Example 4 necessarily comprises a "homogeneous matrix" as required by the amended and allowed claims. The possibility that it might result, or the fact that homogeneity can be an obvious goal of the hypothetical POSA, does not provide written-description.

Third, the proposition that the specification enabled a formulator to make a homogeneous matrix formulation does not mean it described such formulations generally, or showed that the inventors were at the time of filing in possession of the subject matter ultimately claimed.

Finally, the district court succumbed to a circular argument when it accepted Supernus' theory that the working examples satisfied the written-description

[9] The only other disclosure of formulations, Example 1, does not have any that contain all four ingredients, and Dr. Bhatt confirmed that Example 1 disclosed the failed formulations made for Jazz. (Appx238-39 8:53-9:37; Appx12025 111:15-20; Appx12039 125:1-11).

requirement because Supernus had pointed to them when it amended the claims. (Appx131-32). If this were the law, few of the patents found invalid for lack of written description because of unsupported claim amendments would have succumbed. Prosecution counsel's assertion that an amendment is supported does not make it so.[10]

A. The District Court Applied The Wrong Standard In Concluding That the Working Example Provided Adequate Written-Description Support for the Amended Claims Directed to "Homogeneous Matrix" Formulations Generally

As noted above, Supernus abandoned the argument it made during prosecution that the amendment adding "homogeneous matrix" was supported by that phrase in the specification. Accordingly, Dr. Hopfenberg's testimony that there was a complete disconnect between the way "homogeneous matrix" was used in the specification and the way it was used in the claims (Appx13298-13302 1385:22-1389:16) was unrebutted.

Instead, Supernus argued that the claimed formulations were inherently described by the working example because, in the words of its prosecution counsel, "one of ordinary skill in the art would appreciate that the formulations derived

[10] It is the rare patent attorney who does not have as part of her form response and amendment a phrase such as "support for the amendment can be found throughout the specification, more specifically at paragraphs . . . ," and the rare amendment that does not include such an assertion.

according to the protocol set forth in the Examples would necessarily comprise a homogeneous matrix." (Appx26171, citing Appx14089 ¶4) (emphasis added).

The district court committed legal error in finding this sufficient because, even if true, the single working example would be insufficient to support the claims. It also clearly erred in its factual determination that the example necessarily resulted in a "homogeneous matrix" as claimed.

1. Because Example 4 Does Not Describe The Breadth Of "Homogeneous Matrix" Formulations As Claimed, The District Court Erred As A Matter Of Law In Holding That It Was Sufficient

Even if the protocol of Example 4 would necessarily result in a formulation with a "homogenous matrix" within the scope of the claims, the district court committed legal error in finding that this example satisfied the written-description requirement for the amended claims. Supernus used hindsight to pick one purported characteristic of Example 4—a characteristic that is nowhere discussed in that example or elsewhere in the specification—and make it the basis of claims that cover not just the exemplary formulation, but any formulation which has that characteristic (a matrix in which all the ingredients are uniformly dispersed).

A similar attempt was rejected in *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320 (Fed. Cir. 2000), in which the patentee, Purdue, amended its claims to add a pharmacokinetic element (the ratio of C_{max} to C_{24}) said to be based on the working examples. As in the case at bar, however, nothing in the specification

pointed to that ratio as a characteristic of the invention (or even of the examples). As the Court explained, "[a]lthough the examples provide the data from which one can piece together the C_{max}/C_{24} limitation, neither the text accompanying the examples, nor the data, nor anything else in the specification in any way emphasizes the C_{max}/C_{24} ratio." *Id.* at 1326. Accordingly, "one of ordinary skill in the art would not be directed to the C_{max}/C_{24} ratio as an aspect of the invention." *Id.*

In the case at bar, Supernus attempted the same argument as Purdue, which is the erroneous proposition that an unstated characteristic of a working example permits a patentee to broadly claim all other formulations which share that characteristic. As in *Purdue*, there is nothing in the specification that points the hypothetical POSA to this unstated characteristic of the working example. Nor are the claims drawn narrowly to the working example itself: To the contrary, the recitation of the three excipients claimed largely by function, and the lack of specifics as to their amounts (even in the asserted dependent claims), demonstrates the breadth of Supernus' overreach.

2. The District Court Failed To Apply The Correct Standard Of Written Description And Instead Relied Upon An Erroneous Obviousness Standard

The district court also erred in rejecting the written-description defense based on its finding that the working examples could comprise a homogeneous

matrix or that it would be obvious for a formulator to make a homogeneous matrix based on the prior art. The error here is also one of law, *i.e.*, concluding based on these facts that the legal requirement for written description was satisfied. *See Martin v. Mayer*, 823 F.2d 500, 505 (Fed. Cir. 1987) (written description "is a question [of] whether the application necessarily discloses that particular" invention).

Examination of the testimony from the witness on which the district court relied—Actavis's expert Dr. Hopfenberg—shows that a legally correct finding of compliance with the written-description requirement could not be made based on the examples:

> Q. … Now, going back to DDX-14.28 and the portion of the specification Column 10, lines 32 to 56. Does this portion of this specification indicate to you that one of ordinary skill in the art would find that the applicants were in possession of the invention as later claimed?
>
> A. It would not.
>
> Q. Why not?
>
> A. It gives a very general description of a process. It might be the objective of that process to have a uniform matrix, but there is nothing in here that points directly to these particular process variables would lead in this direction. There is no discussion of what's meant by "dry powders." There is no characterization of size, shape, distribution of sizes, distribution of shapes, so the various individual components that compose dry powders. All of these things would be critically important to the formation of a homogeneous matrix.

> Q. Now, is it plausible that this could result in a homogeneous matrix as ultimately claimed?
>
> A. Yes.
>
> Q. And does it necessarily do so?
>
> A. It certainly doesn't.

(Appx13308 1395:3-24). Similarly, a second Actavis expert (Dr. Muzzio) testified that "I think a person of ordinary skill in the art at least looking at the examples in the patent may conclude that this may result in a homogenous matrix, although not necessarily." (Appx12886 972:8-10).

Nor does Dr. Hopfenberg's testimony that the prior art rendered obvious the goal of a homogeneous matrix (Appx13342 1429:1-10) support the legal conclusion that the Supernus specification described such formulations as claimed. The district court cited the following testimony from Dr. Hopfenberg in support of written description of "homogeneous matrix."

> Q. …Would you agree that absent a specific objective not to be homogeneous, the default objective for a pharmaceutical formulator would be to create a homogeneous matrix formulation that would comprise a uniform dispersion of ingredients?
>
> A. I think that would be an obvious objective of the skilled formulator.
>
> Q. So you would agree with that statement?
>
> A. I would.

> Q. You would also agree that the objective of the person of ordinary skill in the art forming such a matrix device would be to form a homogeneous matrix in the absence of any disclaimer to the contrary. Do you agree with that statement?
>
> A. I believe I would give the same answer I did before, the person of ordinary skill in the art formulating a matrix-based formulation -- the person of ordinary skill in the art developing a matrix-based formulation would have as an objective the formation of a homogeneous matrix.

(Appx13406 1493:12-1494:4). Clearly, Dr. Hopfenberg was not even testifying about the written description of the patents. Moreover, his opinions regarding the obviousness of "homogeneous matrix" is legally insufficient to prove written description. *See Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("the question is not whether a claimed invention is an obvious variant of that which is disclosed in the specification"); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998) (disclosure "that merely renders the . . . invention obvious is not sufficient to meet the written description requirement").

3. The District Court Improperly Applied An Enablement Standard For Written Description

The district court also erred in rejecting Actavis's written-description defense based on its finding that the claims were enabled, again an error of law. Actavis did not assert a non-enablement defense at trial.

Whereas the written-description requirement ensures "that the patentee had possession of the claimed invention at the time of the application, *i.e.*, that the patentee invented what is claimed," *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-45 (Fed. Cir. 2005), the enablement inquiry is whether one of skill of the art would be able to make and use the full scope of the invention as claimed after reading the specification without undue experimentation. *See In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). And of course, a claim can be enabled but not described. "Such can occur when enablement of a closely related invention A that is both described and enabled would similarly enable an invention B if B were described." *See Univ. of Rochester v. GD Searle & Co.*, 358 F. 3d 916, 921-922 (Fed. Cir. 2004).

The district court erroneously applied the enablement standard in finding written description. Relying on Example 4 and Dr. Hopfenberg's testimony, the district court concluded:

> Actavis argues that Supernus's reliance upon Dr. Hopfenberg's testimony is misplaced because Dr. Hopfenberg simply described in general terms what a person skilled in the art would like to achieve in a formulation, that is, a homogeneous matrix, and not the invention. This Court disagrees. The specification sets forth the manufacturing process in Example 4 how to produce a homogeneous matrix.

(Appx133) (emphasis added). Again, this finding of fact (even if accepted) does not negate the written-description defense.

IV. The Asserted Claims Are Invalid Because "Homogeneous Matrix" Is Indefinite

The statute's requirement of definiteness, 35 U.S.C. § 112(b), mandates that claims are "precise enough to afford clear notice of what is claimed." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). The standard for compliance is that the "patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." *Id.*

A. Supernus' Own Expert Established Indefiniteness By Testifying That The Test For Infringement Was Largely Subjective And Arbitrary, And Neither Established In The Art Nor Specified By The Patents-In-Suit

In their effort to stretch "homogeneous matrix" around the Actavis tablets, Supernus' own expert proved this element indefinite. Dr. Bugay was tendered as an expert by Supernus in the use of Raman imaging to determine the location of ingredients within pharmaceutical products. (Appx12231 317:10-22). He displayed his Raman images of the Actavis tablets, opined that they had a homogeneous matrix (purportedly under the district court's construction of "uniformly dispersed") (Appx12232-34 318:24-320:9; Appx12252-12259 338:9-345:24), and volunteered how he reached that conclusion:

> And I think it's important to understand how I made that visual assessment.

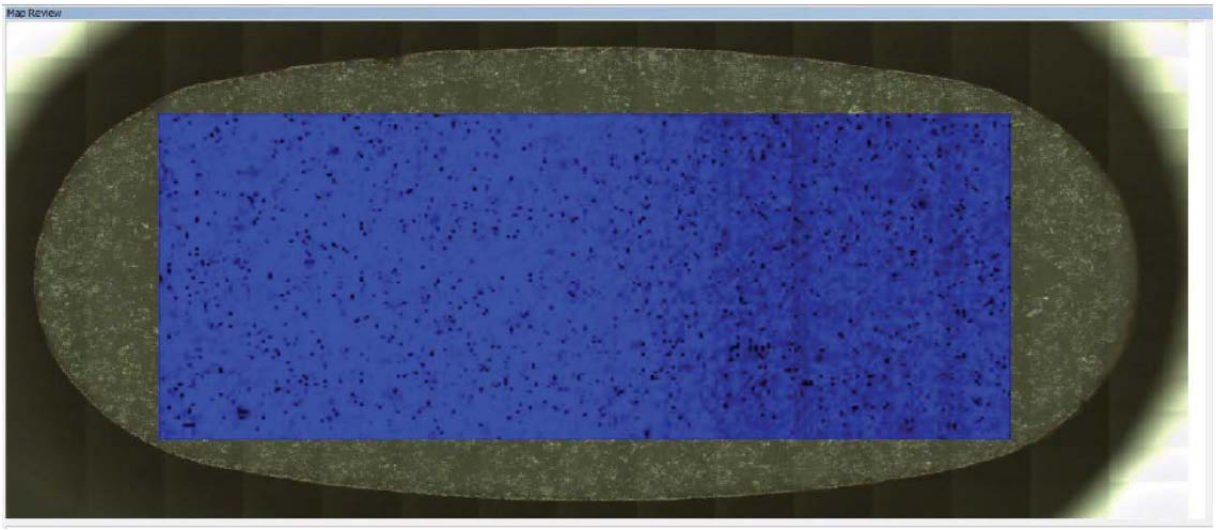
> If we go back to the oxcarbazepine image for a minute, as you look at this, I don't see that the active here is localized in one area. For instance, I don't see that all the pixels are in the upper right corner. Okay? I don't see that all the blue pixels are smack in the middle of the image. I see that the pixels are dispersed throughout the entire image. All right? And, given my pharmaceutical experience, 30 years of looking at tablets and such, I look at that as being uniformly dispersed.
>
> Now, having said that, you know, in the pharmaceutical industry, we don't have the precision of a mason, for example, to lay a brick wall and have the bricks end to end, end to end, to have a perfect pattern of a brick wall, whether it's end to end or whether it's herringbone, okay? The objective of formulators in generating or creating a pharmaceutical manufacturing process is to create, okay, a consistent homogeneous product, okay? Do we get it perfect? No. We have limitations in that.
>
> From my assessment of looking at images and homogeneity, I look at this as I just said: Do we have a localization? No, we don't. We can see that those pixels representing oxcarbazepine are dispersed uniformly throughout that two-dimensional area.

(Appx12255-56 341:3-342:3).

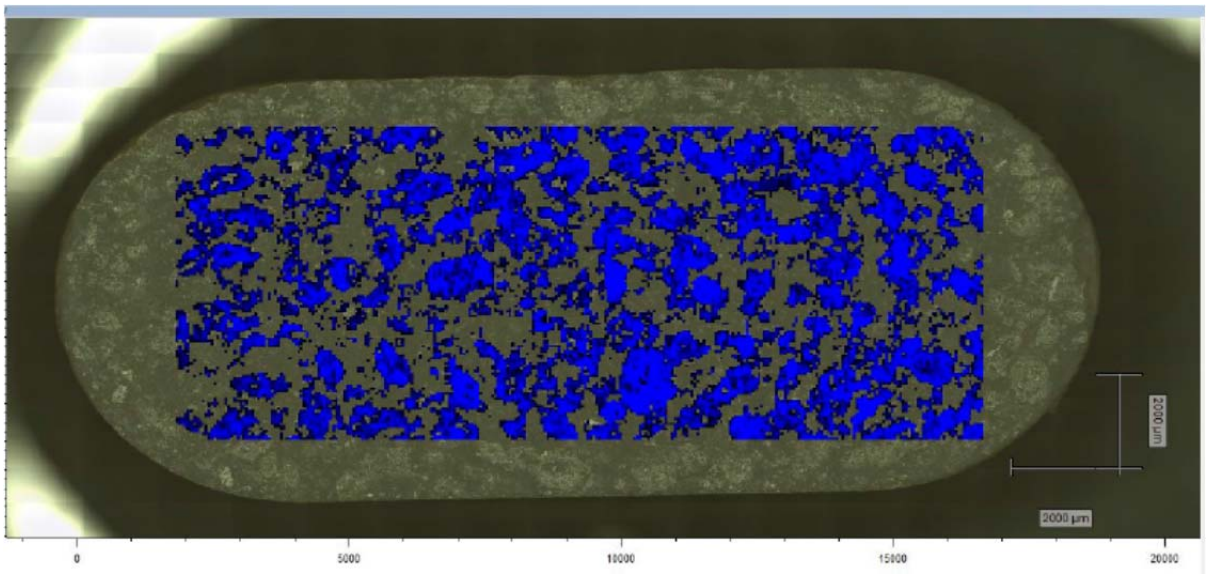
The subjective and arbitrary nature of this claim limitation was further brought out by Dr. Bugay on cross-examination, when he retreated to the proposition that "uniform distribution" in his understanding meant different things different pharmaceuticals, depending on the "particular product" and "particular process." (Appx12285-86 371:25-372:5). He then suggested that the standard was somewhere between perfection (like bricks in a wall) and a tablet that would

contain the same amount of drug in each half if the patient were to snap it in two. (Appx12287 373:3-22). Continuing, he suggested that a tablet that contained drug in each of four quadrants might satisfy the requirement, but required a "mental process" to further consider the distribution. (Appx12288-89 374:9-375:6).

When asked to compare his Raman imaging of the oxcarbazapine in each of Oxtellar and the Actavis products, Dr. Bugay denied there was any difference in homogeneity between these two images. (Appx12290 376:3-12).



(Appx23242) (Oxcarbazepine in Oxtellar XR),



(Appx23219) (Oxcarbazepine in the Actavis tablet).

He justified this by testifying that the ingredients and manufacturing processes were different, and stated that they were uniformly dispersed "on a different level." (Appx12290-91 376:19-377:18).

Finally, Dr. Bugay resisted comparing his Raman images of the Actavis tablet with images from an article in the *International Journal of Pharmaceutics* that characterized the excipients as "not a very homogeneous distribution" by complaining that everyone had different approaches, and that he "worked off the patent and the patent did not describe a specific means of doing the interpretation:"

> That's the point. The all of this data is what it is. I understand that. I understand, you know, this agglomeration and such, but these are different APIs, different pharmaceutical processes, and obviously different perspectives. If you were doing an apple to apple comparison, then we could make something more out of it.

> And also, these are articles about different approaches that one can take in terms of interpreting images. I worked off the patent and the patent did not describe a specific means of doing the interpretation, and so from a person skilled in the art of doing 30 years of analysis we look visually at these images. And that's what they did too.

(Appx12317 403:12-23).

Beyond admitting that there was no standard in the patent, Dr. Bugay's testimony also made clear that there is no generally recognized standard in the art that can be used to determine if a tablet has a "homogeneous matrix," since when confronted with similar chemical images of other products—including some in a publication from his own former company SSCI—he abjured the proposition that they could be used to answer the question in the case at bar. (*Id.*; *see also* Appx12334 420:1-11).

Even under the Federal Circuit's pre-*Nautilus* standard for indefiniteness, the boundaries of the claims could not turn on the intent of the purported infringer or his or her subjective preferences. *See Datamize LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1350, (Fed. Cir. 2005). But here, Dr. Bugay's testimony indicated that each product would have to be evaluated using a different standard, and that one would have to know what the manufacturer of the product intended. (Appx12317 403:12-23). To be sure, the need for a product-specific standard would by itself not be problematic if the patent described that standard, but Dr.

Bugay testified that it did not. (*Id.*) Nor is it consistent with basic principles of patent law to posit that identical products might be either infringing or noninfringing based on the intent of the person who made them. *See Global-Tech Appliances, Inc. et al. v. SEB S.A.*, 563 U.S. 754, 760-61, n.2 (2011).

B. The District Court Applied An Incorrect Legal Standard In Rejecting The Indefiniteness Defense

The reasons articulated by the district court for rejecting Actavis' defense that the claims were invalid as indefinite were erroneous, either because they applied an incorrect legal standard or an incorrect claim construction.

First, the district court reasoned that "homogeneous matrix" is definite because one of skill in the art would understand that "homogeneity varied in degrees." (Appx137). But the fact that it varies proves indefiniteness absent an objective standard provided by the intrinsic evidence. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1218 (Fed. Cir. 1991); *see also Datamize,* 417 F.3d at 1351-52.

Second, the district court erred in rejecting the defense based on its finding that a skilled worker "could turn to FDA uniformity testing to confirm that a particular manufacturing process worked as intended" to determine the scope of the claims. (Appx138). As discussed above, however, there was no basis to import regulatory standards or guidelines into the construction of "homogeneous matrix." (*vide supra* I.C). Nor would compliance with FDA standards satisfy this

element of the claims even under Supernus' view, given the testimony of its expert Dr. Little that enteric coated tablets—which clearly do not comprise a homogeneous matrix and are the "antithesis" of the invention—would satisfy FDA standards for uniformity. (Appx12633-35 719:15-721:20).

Third, there is no evidence to support the district court's reliance on Example 4 as setting forth the metes and bounds of "homogeneous matrix," because that example provides no standard by which to judge whether the ingredients in any given formulation are or are not "uniformly dispersed." Nor, of course, can "homogeneous matrix" be construed to mean any formulation made in a manner that is similar to Example 4.

This case is particularly analogous to *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364 (Fed. Cir. 2014), where this Court rejected the patentee's argument that "unobtrusive manner" was definite because it was tied to examples in the specification. It was not enough to say that an example met the claim limitation; the patent had to define how the embodiments were related to the claim language, *i.e.*, what part of the embodiment in the specification was an "unobtrusive manner" and why. *Id.* at 1372.

Finally, the district court seemed to recognize that Supernus' chemical imaging evidence showed there was no recognizable standard in the art that sets a clear line between a matrix that is homogeneous and one that is not. (Appx137). It

was legal error to not find that the claims were indefinite because of this fact, because "homogeneous matrix" is a term of structure requiring that all ingredients within the matrix be uniformly dispersed, and chemical imaging was the only way elucidated at trial to show how the ingredients within the accused tablets are actually dispersed. If the best test for uniformity has no standard, the claims are indefinite.

CONCLUSION AND STATEMENT OF RELIEF

The Court should reverse the judgment of infringement because the accused Actavis tablets contain neither a "homogeneous matrix" nor "an agent that enhances the solubility oxcarbazepine," or in the alternative, remand for a new trial based on the proper construction of these terms.

The Court should also reverse the judgment that the asserted claims are not invalid.

Dated: May 9, 2016

Respectfully submitted,

By: /s/ *Charles A. Weiss*

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ADDENDUM

ADDENDUM

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ORDERS AND JUDGMENT

PATENTS-IN-SUIT

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

SUPERNUS PHARMACEUTICALS INC., Plaintiff, v. ACTAVIS INC. et al., Defendants.	Civil No. 13-4740 (RMB/JS) **ORDER OF JUDGMENT**
SUPERNUS PHARMACEUTICALS INC., Plaintiff, v. ACTAVIS INC. et al., Defendants.	Civil No. 14-1981 (RMB/JS) **ORDER OF JUDGMENT**

BUMB, UNITED STATES DISTRICT JUDGE:

THIS MATTER having been tried before this Court; and

THE PARTIES having completed post-trial briefing; and

FOR THE REASONS set forth in the accompanying bench Opinion;

IT IS HEREBY on this **5th** day of **February 2016**,

ORDERED that the Defendants' manufacture and sale of its generic products, as described in ANDA No. 205444, will INFRINGE U.S. Patent No. 7,722,898 (the "'898 Patent"); and it is further

ORDERED that the ’898 Patent is VALID; and it is further

ORDERED that the Defendants’ manufacture and sale of its generic products, as described in ANDA No. 205444, will INFRINGE U.S. Patent No. 7,910,131 (the “’131 Patent”); and it is further

ORDERED that the ’131 Patent is VALID; and it is further

ORDERED that the Defendants’ manufacture and sale of its generic products, as described in ANDA No. 205444, will NOT INFRINGE U.S. Patent No. 8,617,600 (the “’600 Patent”); and it is further

ORDERED that the Defendants’ remaining oral motion for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c) is GRANTED as to the ’600 Patent; and it is further

ORDERED that the ’600 Patent is VALID; and it is further

ORDERED that the Plaintiff’s renewed motion to exclude the deposition testimony of Dr. Irwin Jacobs at trial is DENIED AS MOOT, since the evidence to which it pertained was not material to the Court’s findings of fact and conclusions of law; and it is further

ORDERED that the Plaintiff’s renewed motion to preclude the Defendants from arguing that its generic products lack an element 1(c) agent that enhances the solubility of oxcarbazepine is DENIED WITH PREJUDICE for the reasons set forth in the accompanying Opinion; and the Court further notes that the

remaining motions to seal will be addressed separately; and it is further

ORDERED that the Sealed Opinion accompanying this Order shall be filed UNDER SEAL, while the Redacted Opinion shall be PUBLICLY FILED.

s/Renée Marie Bumb_
RENÉE MARIE BUMB
UNITED STATES DISTRICT JUDGE

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

SUPERNUS PHARMACEUTICALS INC., Plaintiff, v. ACTAVIS INC. et al., Defendants.	Civil No. 13-4740 (RMB/JS) **OPINION** **(PUBLICLY FILED)**
SUPERNUS PHARMACEUTICALS INC., Plaintiff, v. ACTAVIS INC. et al., Defendants.	Civil No. 14-1981 (RMB/JS) **OPINION** **(PUBLICLY FILED)**

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BUMB, UNITED STATES DISTRICT JUDGE:

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I. INTRODUCTION

This is an action for patent infringement brought by Plaintiff Supernus Pharmaceuticals, Inc. ("Supernus" or "Plaintiff") against Defendants Actavis Inc., Watson Laboratories, Inc. - Florida n/k/a Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Watson Laboratories, Inc., and ANDA, Inc. (collectively, "Actavis" or "Defendants") pursuant to 35 U.S.C. § 271(e)(2)(A) and §§ 271(a), (b), and (c).

This case involves Supernus's Oxtellar XR® product, a once-daily extended release oxcarbazepine tablet used to treat partial epilepsy seizures in adults and children above the age of six. Supernus seeks to prevent the Defendants from selling a generic version of Oxtellar XR®, in connection with Actavis's submission of Abbreviated New Drug Application ("ANDA") number 205444 seeking the approval of the U.S. Food & Drug Administration ("FDA") to market its generic ANDA product (the "Actavis Tablets") prior to the expiration of certain patents held by Supernus. Specifically, Supernus alleges that in selling its generic version of Oxtellar XR®, the Defendants will infringe U.S. Patent Nos. 7,722,898 (the "'898 Patent"), 7,910,131 (the "'131 Patent"), and 8,617,600 (the "'600 Patent") (collectively, the "Supernus Patents" or the "Patents-in-Suit").

Supernus is asserting claims 1, 6 to 8, 11, 18, and 19 of the '898 Patent, claims 6 to 8, 11, 18, 19, and 21 of the '131

Patent, and claims 1, 7 to 9, 12, 18, and 19 of the '600 Patent. The asserted claims all require a homogeneous matrix comprising the active pharmaceutical ingredient oxcarbazepine, a matrix forming polymer, a solubility enhancing agent, and a release promoting agent. Claim 1 of the '898 Patent provides:[1]

> 1. A pharmaceutical formulation for once-a-day administration of oxcarbazepine comprising a homogeneous matrix comprising:
>
> (a) oxcarbazepine;
>
> (b) a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;
>
> (c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and
>
> (d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, and Eudragit L 100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers.

[1] Although the '898, '131, and '600 Patents share the same specifications, they are slightly different. For convenience, citations to the specifications of the Patents-in-Suit are to the '898 Patent, unless otherwise noted.

The dependent claims of the '898, '131, and '600 patents generally specify the types of excipients for the matrix forming polymer, solubility enhancing agent, and release promoting agent. They also specify the ranges of fluctuation in pharmacokinetic parameters.

The Court conducted a seven-day bench trial from November 18, 2015 through December 4, 2015. It then permitted the parties to file post-trial briefing.[2]

After considering all the evidence, and for the reasons set forth below, the Court finds that: (1) the Defendants will infringe the '898 Patent and the '131 Patent; (2) the Defendants will not infringe the '600 Patent; and (3) all the Patents-in-Suit are valid. Accordingly, the Court enters judgment against Actavis and in favor of Supernus as to the '898 and '131 Patents and against Supernus and in favor of Actavis as to the '600 Patent. This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Rule 52(a).[3]

[2] The Court expresses its appreciation to counsel for their professionalism and valuable contributions to this litigation.

[3] The Defendants' oral motion made during trial for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c) is GRANTED as to the '600 Patent only. Rule 52(c) permits such motions after "a party has been fully heard on an issue during a nonjury trial." During trial, the Court denied the motion as to the '898 and the '131 Patents, but exercised its discretion to reserve on the motion as to the '600 Patent. Tr. 879:4-8.

II. BACKGROUND[4]

A. The Drug Approval Process

Under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq., the FDA must approve all new drugs before they may be distributed in interstate commerce. 21 U.S.C. § 355(a). To secure approval for a new drug, an applicant may file a New Drug Application ("NDA") that includes, inter alia, the number and expiration date of any patents which claim the drug or a method of using the drug if a claim of patent infringement could reasonably be asserted. Id. § 355(b)(2). "The FDA publishes the names of approved drugs and their associated patent information in the Approved Drug Products with Therapeutic Equivalence Evaluations list, commonly referred to as the 'Orange Book.'" AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1045 (Fed. Cir. 2010). An applicant seeking approval to market a generic version of a drug that has already been approved may file an ANDA, which "allows an applicant to rely on the safety and efficacy information for the listed drug if the applicant can show that the generic drug is 'bioequivalent' to the listed drug." Id. (citing 21 U.S.C. §§ 355(b)(2), 355(j)).

[4] Because this civil action arises under the United States patent laws, Title 35 of the United States Code, this Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

"[F]or each patent listed in the Orange Book that claims either the listed drug or a use of the listed drug for which the applicant is requesting approval, an ANDA must include either one of four certifications or a 'section viii statement.'" AstraZeneca LP, 633 F.3d at 1046. If an applicant submits a certification, the applicant must certify "(I) that . . . patent information has not been filed, (II) that such patent has expired, (III) . . . the date on which such patent will expire, or (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug." 21 U.S.C. § 355(j)(2)(A)(vii)(I)—(IV). The last of these is known as a "paragraph IV certification." If an ANDA applicant submits a paragraph IV certification and a patent infringement suit is commenced within 45 days, then the FDA may not approve the ANDA application until the expiration of a 30-month statutory period. Id. § 355(c)(3)(C).

B. Epilepsy and the Anti-Epilepsy Drug Market

Epilepsy is a serious and chronic neurological disorder characterized by seizures. It cannot be cured, but it can be managed by anti-epileptic drugs ("AEDs"). Trial Transcript ("Tr.") 1195:20-1196:7 (Wheless Direct). Seizure control, through medication, is crucial and often challenging to achieve. Likewise, patients' compliance with their medication regimen is paramount given the potentially devastating consequences of a

patient not taking the medication properly. Id. at 1201:4-1202:15. Once a physician has established an effective AED regimen for a given patient, the physician will likely be reluctant to change the regimen for fear of breakthrough seizures or changes in the patient's tolerability for the medication. See, e.g., Tr. 1517:19-1519:1 (Rausser Direct); Tr. 1257:4-5 (Lado Direct).

Prior to the commercial release of Oxtellar XR®, there were over twenty different types of AEDs available on the market worldwide. Tr. 1242:24-1243:2 (Lado Direct). These included oxcarbazepine formulations, as well as medications with different active ingredients, such as carbamazepine. Some AEDs had already been reformulated for extended release. Id. at 1242:24-1243:6, 1244:24-1245:12. Oxcarbazepine, however, had not. Additionally, the available AEDs at the time utilized varying mechanisms or modes of action. Id. at 1243:8-15; DTX 471 at ACT-OXXR002757935. Twice daily oxcarbazepine first entered the market as branded Trileptal® in 2000. Several generic versions followed. Id. at 1241:17-1242:1.

C. Supernus's Oxcarbazepine Drug Oxtellar XR® and the Patents-in-Suit

1. The Patents-in-Suit

The Patents-in-Suit describe and claim a specific type of oxcarbazepine formulation for the treatment of seizures with a

"homogenous matrix" containing the active ingredient, oxcarbazepine, and excipients. The "homogeneous matrix" is central to the claimed invention.

a) The '898 Patent

On May 25, 2010, the United States Patent and Trademark Office (the "PTO") issued the '898 Patent, entitled "Modified-Release Preparations Containing Oxcarbazepine and Derivatives Thereof." PTX 1. The named inventors are Dr. Padmanabh P. Bhatt, Dr. Argaw Kidane, and Dr. Kevin Edwards. The '898 Patent was filed on April 13, 2007 as Application No. 11/734,874 and is related to Provisional Application No. 60/794,837, filed on April 26, 2006. The '898 Patent expires on April 13, 2027.

The '898 Patent covers an oxcarbazepine formulation administered once-daily for the treatment of seizures. Supernus asserts that before the '898 Patent, there were no once-daily oxcarbazepine tablets for the treatment of seizures. Tr. 56:4-60:13 (Bhatt Direct); PTX 1.17 at col. 1, ll. 20-col. 2, ll. 16. Although oxcarbazepine had been available for use twice daily in immediate-release form, there were no clinical studies showing that it would be effective once daily.

b) The '131 Patent

The '131 Patent, entitled "Method of Treating Seizures Using Modified Release Formulations of Oxcarbazepine," was filed on August 27, 2008 as Application No. 12/230,276, which was a

continuation of Application No. 11/734,874, filed on April 13, 2007. The '131 Patent is also related to Provisional Application No. 60/794,837, filed on April 26, 2006. The '131 Patent was issued by the PTO on March 22, 2011 and expires on April 13, 2027. The '131 Patent covers a method of treating seizures by administering an oxcarbazepine pharmaceutical formulation.

c) The '600 Patent

The '600 Patent, entitled "Modified Release Preparations Containing Oxcarbazepine and Derivatives Thereof," was filed on May 21, 2012 as Application No. 13/476,337, which was a continuation of Application No. 13/137,382, filed on August 10, 2011, which was in turn a continuation of Application No. 12/230,275, filed on August 27, 2008, which is a continuation of Application No. 11/734,874, filed on April 13, 2007. The '600 Patent is also related to Provisional Application No. 60/784,837, filed on April 26, 2006. The '600 Patent was issued by the PTO on December 31, 2013 and it expires on April 13, 2027. The '600 Patent also covers an oxcarbazepine formulation for the treatment of seizures. Its terms are largely similar to those of the '898 Patent but also include certain percentages by weight of the formulation and *in vitro* dissolution limitations.

The Defendants dispute Supernus's claims relating to the each of the Patents-in-Suit on grounds of non-infringement and invalidity.

2. Oxtellar XR®

In October 2012, the FDA approved NDA No. 202810 for an oxcarbazepine extended-release oral tablet, which Supernus markets under the name Oxtellar XR®. Its sole active ingredient is oxcarbazepine, an anti-epileptic drug that has been known for almost 50 years. Oxtellar XR® is indicated for the treatment of seizures in adults and children above six years of age. Stipulated Facts ("SF") [Docket No. 353] p. 6 ¶ 1; PTX 388.1. Oxtellar XR® contains oxcarbazepine in an extended release formulation that is intended to be taken less frequently than immediate-release oxcarbazepine. SF p. 6 ¶ 3.

The Patents-in-Suit cover the once-a-day oxcarbazepine formulation embodied by Oxtellar XR® and the use of this formulation. Tr. 1635:5-1641:17 (Little Direct); Tr. 1690:17-1692:13 (Thakker Direct); Tr. 355:6-357:13 (Bugay Direct); PTX 388.

Supernus launched Oxtellar XR® on February 1, 2013. SF p. 13 ¶ 34. At the time of its release, and to this day, Oxtellar XR® is the only FDA-approved oxcarbazepine formulation for once-a-day administration for the treatment of seizures. SF p. 6 ¶ 3, p. 13 ¶ 35. Prior to the commercial release of Oxtellar XR®,

oxcarbazepine was available only in immediate release, twice daily formulations. Trileptal®, the brand name twice daily oxcarbazepine formulation, was released in 2000 and generic versions followed. As a once daily oxcarbazepine formulation, Oxtellar XR® overcame certain difficulties presented by the immediate release, twice daily medications available at the time, including concerns regarding patient compliance, fluctuations in blood plasma concentration, and disruptive side effects.

D. Actavis's ANDA

On March 20, 2013, less than two months after the commercial launch of Oxtellar XR®, Actavis filed ANDA No. 205444 with the FDA seeking regulatory approval to market extended-release oxcarbazepine oral tablets in 150 mg, 300 mg, and 600 mg dosages. Actavis's ANDA identifies the listed drug product that is the basis for the submission as Oxtellar XR®. Actavis's ANDA included a paragraph IV certification asserting that the '898, '131, '600 Patents are invalid, unenforceable, or will not be infringed by the manufacture or sale of its generic extended-release oxcarbazepine tablets. Actavis's ANDA is currently pending.

III. LEGAL ANALYSIS

To prove infringement, the patentee must show that it is more likely than not that the proposed ANDA product would, if

commercially marketed, meet all of the claim limitations of the Patents-in-Suit. See Adams Respiratory Therapeutics, Inc. v. Perrigo Co., 616 F.3d 1283, 1287 (Fed. Cir. 2010) (en banc); Abbot Labs. v. TorPharm, Inc., 300 F.3d 1367, 1373 (Fed. Cir. 2002) (infringement analysis turns on whether accused product satisfies every limitation of the claim in question). In other words, the patentee "has the burden of proving infringement by a preponderance of the evidence." Kegel Co., Inc. v. AMF Bowling, Inc., 127 F.3d 1420, 1425 (Fed. Cir. 1997); SmithKline Diagnostics, Inc. v. Helena Labs. Corp., 859 F.2d 878, 889 (Fed. Cir. 1988). Determining whether an accused product infringes the patent involves a two-step analysis. Kegel, 127 F.3d at 1425. The Court must first construe the scope and meaning of the asserted patent claims and then compare the accused product to the properly construed claims. Id.

Before beginning this two-step analysis, the Court observes that, although the parties do not agree on the definition of a person of ordinary skill in the art, sometimes referred to as a POSA, compare Joint Final Pre-Trial Order [Docket No. 353], p. 41 ¶ 152, with id. at p. 99 ¶ 173,[5] they have made no arguments

[5] Supernus proposes the following definition of a person of ordinary skill in the art:

> a person in the 2006 time frame with at least a Bachelor of Science Degree in Pharmaceutical Sciences or a related field and approximately 3-5 years of experience in the

as to which definition the Court should adopt. Furthermore, the parties have not identified how the Court's analysis would differ depending on the definition adopted. Nonetheless, the Court sees no material difference between the definitions put forth by the parties and finds that its claim construction, infringement, and validity analyses would be the same under either definition.

> field of drug delivery technology or a related field (or a person of commensurate education and experience).

Joint Final Pre-Trial Order, p. 41 ¶ 152.

Actavis, in turn, proposes the following definition of a person of ordinary skill in the art:

> The person of ordinary skill in the art is engaged in the design and development of extended-release dosage forms. The person of ordinary skill in the art has at least a B.S. degree in the biological, chemical, or pharmaceutical sciences, or materials science or chemical engineering, and several years of experience in the field of pharmaceutical formulation development, with the amount of post-graduate experience depending upon the level of formal education obtained. Further, the person of ordinary skill in the art may possess the knowledge of a collaborative team of ordinarily skilled artisans in related disciplines of pharmaceutical sciences that would work together in the relevant field. The person of ordinary skill in the art would either have his or her own education and experience in the fields of pharmaceutics and pharmacodynamics or be part of a team that includes a skilled artisan in the fields of pharmacokinetics and pharmacodynamics. Therefore, for the elements in the patent claims that address pharmacokinetics and/or treatment-related limitations, the skilled formulator would have ready access to and the ability to communicate with one of ordinary skill in the art of pharmacokinetics and pharmacodynamics.

Id. at p. 99 ¶ 173.

A. Claim Construction

As for the first step, on August 14, 2014, the parties filed their Joint Claim Construction and Prehearing Statement pursuant to Local Patent Rule 4.3 and the Court's June 4, 2014 Scheduling Order [Docket No. 138]. On December 9, 2014, the Court conducted a Markman hearing [Docket No. 177]. Although the parties disputed the construction of several claim terms, the Court found that most terms required no construction. There were, however, two terms that required construction: "homogeneous matrix" and "C_{min} and C_{max}."[6]

Claim construction is a question of law. See Markman v. Westview Instruments, Inc., 517 U.S. 370, 391 (1996). The Court determines the meaning of disputed claim terms as understood by one of ordinary skill in the art at the time of invention. See Phillips v. AWH Corp., 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). Claim terms generally should be given their ordinary and customary meaning to a person of skill in the art at the time of the invention. See id. To determine the ordinary meaning, the Court first looks to the intrinsic evidence, which includes the claims, the specification and the prosecution history. Id. at 1312–17 ("Like the specification, the

[6] The Court also construed "once-a-day administration" to mean "administered once per day every 24 hours."

prosecution history provides evidence of how the PTO and the inventor understood the patent.").

The starting point for claim interpretation is the claim language itself, which can "provide substantial guidance as to the meaning of particular claim terms." Id. at 1314. Thus, the language of the claims is paramount. Pass & Seymour, Inc. v. Int'l Trade Comm'n, 617 F.3d 1319, 1324 (Fed. Cir. 2010); see Chef Am., Inc. v. Lamb-Weston, Inc., 358 F.3d 1371, 1374 (Fed. Cir. 2004) ("in accord with our settled practice we construe the claim as written, not as the patentees wish they had written it"). The claims, however, "must be read in view of the specification, of which they are a part." Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir.), aff'd, 517 U.S. 370 (1996). Extrinsic evidence, such as dictionaries, may be consulted to assist in understanding disputed terms. Phillips, 415 F.3d at 1318. Extrinsic evidence, however, must be "considered in the context of the intrinsic evidence." Id. at 1317-19.

1. Homogeneous Matrix

The Court construed the term "homogeneous matrix" as "a matrix in which the ingredients or constituents are uniformly dispersed." The parties had proposed the following construction:

Claim Term	Supernus's Construction	Actavis's Construction
"homogeneous matrix"	"a substantially uniform dispersion of one or more constituents in a given volume" [alternate construction] "matrix in which the constituents are homogeneously dispersed"	"matrix in which the ingredients have a uniform distribution"

Supernus initially argued that a person skilled in the art would understand that the adjective "homogeneous" required substantial uniformity of the matrix constituents rather than complete uniformity on a molecular level. By requiring a "substantially uniform dispersion," Supernus argued, the claim language avoids requiring an unachievable absolute condition. In post-Markman briefing, and upon an unrebutted record that complete uniformity on a molecular level was not possible (or even desired)[7], Supernus provided an alternate construction:

[7] Dr. Steven Little's testimony that a person skilled in the art would understand that complete molecular uniformity is not possible or even desired in pharmaceutical formulations was essentially unrebutted. See Markman Tr. 73:14-74:8 [Docket No. 179]:

> Q. Professor, why are you focusing on this distinction of complete or molecular uniformity?
>
> A. Well, I can imagine processes where you could achieve molecular uniformity, complete uniformity where everything is dissolved and then crystalized, or something together where you would get like perfect arrangement or order, but that's -- you know, we don't use those kind [sic] of processes to make especially solid oral dosage forms here. The types of processes

"matrix in which the constituents are homogeneously dispersed." Pl. Supp. Claim Construction Br. at 4 [Docket No. 192].

Supernus's initial proposed construction is problematic. First, it adds language to the claim — the word "substantially" — that does not appear in the claim and has no support in the intrinsic evidence. Second, it reads the "matrix" limitation out of the claim. That is, under Supernus's initially proposed construction, there is no requirement that the element be in the form of a matrix. There is no need to write out the term "matrix," however, as there is no genuine dispute among the parties that the term excludes the coating or outer core. Indeed, Defendants' own proposal is a "matrix in which" the ingredients are dispersed.

> that are used in the patents-in-suit and common in the field are, like I said, they are mechanical agitation, it's -- it's in one way kind of similar to what you'd see with a kitchen mixer, you know, where you are adding sugar and a whole bunch of things together to make cookies. You know, you get things that end up sticking together because of the egg, which is kind of like the binder. But you end up getting two sugar particles sticking to each other. It's just sort of the way it works. It doesn't disperse out perfectly like that.
>
> So I just felt it was important to help the Court to understand that you can't get that kind of uniformity using these processes that are very standard, nor do you really need to get that kind of uniformity. As long as it's substantially uniform it functions just fine.

The prosecution history elucidates why the term "homogeneous" was added to the claim to exclude the coating: to clarify that, unlike the prior art identified by the Patent Examiner, the claimed formulation was contained in a homogeneous matrix. The Patent Examiner broadly construed the term "matrix" to include the coating of the tablet. PTX 5.281. Supernus took issue with such a broad construction, arguing that a person of ordinary skill in the art would not understand the term matrix to include the coating but rather a pharmaceutical composition wherein the components were "*contained in the matrix*." PTX 5.267 (emphasis in original). The Patent Examiner disagreed, writing that "the term 'a matrix comprising' in amended Claim 1 is not limited to a homogeneously admixed mixture of the four components, as inferred by Applicant's reply." PTX 5.281. Because the claim did not limit it as such, the Examiner rejected it. What followed was Supernus's proposal to amend the claim "to include language which specifies that the components of the pharmaceutical formulation are in a homogeneous admixture." PTX 5.289 (emphasis added). This amendment was viewed by the Examiner as "promising" to overcome the rejection. Id. Supernus thereafter amended the claim to a pharmaceutical

formulation comprising a "homogeneous matrix," which the Examiner allowed.[8] PTX 5.298; PTX 5.406.

Moreover, "substantially" is unnecessary because, as both parties acknowledge, the ordinary meaning of homogeneous is "loosely . . . used to describe a mixture or solution composed of two or more compounds or elements that are uniformly dispersed in each other." Hawley's Condensed Chemical Dictionary 655 (15th ed. 2007) [Docket No. 152-2] (emphasis added). As Hawley's Condensed Chemical Dictionary, cited by both parties, states:

> Actually, no solution or mixture can be homogeneous; the situation is more accurately described by the phrase "uniformly dispersed." Thus so-called homogenized milk is not truly homogeneous; it is a mixture in which the fat particles have been mechanically reduced to a size that permits uniform dispersion and consequent stability.

Hawley's Condensed Chemical Dictionary 577 (14th ed. 2001) [Docket No. 153-5] (emphasis added). See also Webster's II New College Dictionary 542 (3rd ed. 2005) [Docket No. 153-6] ("uniform throughout in structure or makeup"); Grant & Hackh's Chemical Dictionary 286 (5th ed. 1987) [Docket No. 152-2] ("Of uniform or similar nature throughout"); Mosby's Dictionary of

[8] Whether Supernus's amendment to Claim 1 to say "homogeneous matrix" as opposed to "homogeneous admixture" as it had proposed to the Examiner was a malapropism or intended is unclear. See Declaration of Steven R. Little, Ph.D. at p. 23-26 [Docket No. 153-10]. Regardless, the Examiner allowed the claim as amended.

Medicine, Nursing & Health Professions 899 (7th ed. 2006) [Docket No. 152-2] ("having a uniform quality throughout").

The specifications of the Patents-in-Suit support a construction that uses the ordinary term of homogeneous without the qualifier, substantially. Dr. Little explained the high shear granulation manufacturing method disclosed by the Patents-in-Suit in Example 4: the ingredients are added to a high shear granulator; the ingredients are blended by running the blade for three minutes and water is then sprayed onto the "mixing blend," the wet granules are dried in an oven; the dry granules are screened through an 18-mesh screen; the granules are then blended with a lubricant; and tablets are then formed on a rotary tablet press. Tr. 614:14-22 (Little Direct); '898 Patent, col. 10, ll. 37-55; see also id. at col. 5, ll. 5-8 ("The release-promoting agent can be added into the formulation either as a dry material, or it can be dispersed or dissolved in an appropriate solvent, and dispersed during granulation.").

Indeed, Dr. Little appeared to recognize that adding the word "substantially" was not needed.

> THE COURT: But it seems as if you've been saying that it is understood to a person skilled in the art that this perfect uniformity is never achieved. And so, therefore, it seems to me adding the word "substantially" is really not needed because everyone understands exactly what it is that you are saying, that you don't get this perfect uniformity ever; it's impossible.

THE WITNESS: Right. So this is a really good question. Because when I talk to students, for instance, and they are looking at something, you could look at it with your eye and you could think that it's uniform. Right? But then you zoom in a little bit. And I telling [sic] them, you know, look at it with some microscopy and take a look and see what you think. And then they see that. You know, you could see even a distribution of sizes of heterogeneities in the system. So I think it's technically true that a person of ordinary skill would understand that that would be the case. But if you look at the wrong size scale or something like that, you could say oh, look, this is not homogeneous.

THE COURT: But you understand that the test that I use is a person skilled in the art.

THE WITNESS: Hmm.

. . .

THE COURT: Okay. And so it seems to me that in reading the patent, as long as the matrix includes the four things that we've been talking about, the oxcarb, the polymer, the matrix forming polymer, the agent that enhances the solubility and the release promoting agent, as long as those four things are uniformly dispersed in the matrix, that's the matrix.

THE WITNESS: Um-hum.

THE COURT: So you have, you know, one of one, one of two, one of three, one of four. That's uniformity. You are never going to get it perfect, but -- everyone understands you never are going to get it perfect.

THE WITNESS: Um-hum.

THE COURT: And so a person skilled in the art doesn't need to be told "substantially."

THE WITNESS: I think - -

THE COURT: Do you agree with that?

THE WITNESS: Yes.

Markman Tr. 125:10-127:1.

Thus, a "homogeneous matrix" means "a matrix in which the ingredients or constituents are uniformly dispersed."

2. C_{min} and C_{max}

The Court construed C_{min} to mean "minimum concentration in blood or plasma at steady state." The Court construed C_{max} to mean "maximum concentration in blood or plasma at steady state."

The parties had proposed the following constructions:

Claim Term	Supernus's Construction	Actavis's Construction
"C_{min}"	"minimum concentration in blood or plasma at steady-state"	"minimum concentration in blood once steady state is achieved"
"C_{max}"	"maximum concentration in blood or plasma at steady-state"	"maximum concentration in blood"

First, the parties propose nearly identical constructions for C_{min} except that the Defendants' definition refers only to blood rather than blood or plasma. However, the Patents-in-Suit use the words interchangeably. '898 Patent, col. 5, ll. 38-41 ("These types of release profiles ensure that the C_{max} (maximum concentration of the drug in blood/plasma) is kept within the therapeutic window while extending the maintenance of an effective drug level in the body"); '600 Patent, col. 5, ll. 43-47, '131 Patent, col. 5, ll. 42-45. As a further example,

Example 7 explains that the oxcarbazepine and monohydroxy derivative ("MHD") data shown in Figures 12 and 13 was obtained by analyzing "blood samples," '898 Patent, col. 12, ll. 33-37; '131 Patent, col. 12, 11. 32-36; '600 Patent, col. 12, ll. 34-38 (emphasis added), while the Y-axes of Figures 12 and 13 are labeled as "Plasma MHD conc. (µg/ml)" and "Plasma OXC conc. (µg/ml)," respectively. '898 Patent, Figs. 12, 13 (emphasis added); '131 Patent, Figs. 12, 13; '600 Patent, Figs. 12, 13; see also Declaration of Dhiren R. Thakker, Ph.D. at ¶ 64 [Docket No. 153-11]. (explaining how the specifications (e.g., Example 7) use the words interchangeably).

As to the remaining dispute, it is clear that C_{max} must be measured under steady state conditions. Actavis's proposed construction does not specify the condition under which C_{min} and C_{max} are to be measured. Moreover, it is clear from the Patents-in-Suit that C_{max} must also be evaluated at steady-state, like C_{min}, for which the Defendants agree. To hold otherwise and adopt the Defendants' proposed construction could lead to the absurd result of C_{max} being less than C_{min}. Accordingly, C_{min} and C_{max} are the minimum and maximum concentration, respectively, in blood or plasma at steady-state.

B. Infringement

As for the second step of the infringement analysis, the Court must determine whether the accused product contains every

limitation of the properly construed claims. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1467 (Fed. Cir. 1998).

1. The ’898 and ’131 Patents

The ’898 and ’131 Patents are directed to "controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration." ’898 Patent, col. 1, ll. 14-16; ’131 Patent, col. 1, ll. 16-18.

Supernus asserts that the Defendants will infringe claims 1, 6 to 8, 11, 18, and 19 of the ’898 Patent and claims 6 to 8, 11, 18, 19, and 21 of the ’131 Patent. Claim 1 of each of the Patents, the only independent claim, requires a "pharmaceutical formulation comprising a homogeneous matrix," which in turns comprises four constituents:

> (a) oxcarbazepine;
>
> (b) a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;
>
> (c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and
>
> (d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-

> maleic mono-ester copolymer, and Eudragit L 100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers. The dependent claims of the '898, '131, and '600 patents generally specify the types of excipients for the matrix forming polymer, solubility enhancing agent, and release promoting agent, and also specify the ranges of fluctuation in pharmacokinetic parameters.

Claim 1 of the '898 Patent additionally requires that the pharmaceutical formulation be "for once-a-day administration." Claim 1 of the '131 Patent discloses a "method of treating seizures" through the administration of the pharmaceutical formulation described above.[9] The remaining asserted claims are all directly or indirectly dependent on Claim 1, meaning that they include all of the limitations of Claim 1 as well as additional limitations.

a) Oxtellar XR®

Supernus's Oxtellar XR® is presently the only commercial embodiment of the Patents-in-Suit available on the market. The parties do not dispute, and the expert testimony at trial confirms, that Oxtellar XR® comprises a homogeneous matrix of the four recited elements. See, e.g., Tr. 960:11-964:1 (Muzzio Cross); Defendants' Proposed Findings of Fact ("DFOF") ¶ 21 [Docket No. 392].

[9] Although Supernus does not assert Claim 1 of the '131 Patent, the asserted claims of the '131 Patent all depend directly or indirectly on Claim 1, and so it must be addressed.

Additionally, Dr. Kidane, one of the inventors on the Patents-in-Suit, testified by video deposition that his understanding of what constitutes a "homogeneous matrix" is that "the components are mixed together." Tr. 463:20-22 (Kidane Depo).[10] He went on to testify that the mixing that takes place during the manufacturing process of the Oxtellar XR® tablets creates homogeneity. Id. at 464:16-465:25. Dr. Little likewise agreed that, when one follows the manufacturing process as set forth in the examples in the Patents-in-Suit, as Supernus does to formulate Oxtellar XR® tablets, a homogeneous matrix is necessarily achieved. Tr. 613:18-614:13 (Little Direct). Dr. Kidane also explained that Supernus conducts uniformity testing on the Oxtellar XR® product to confirm the homogeneity of the

[10] The Court denied the Defendants' application to strike the deposition testimony of Vitaliy Disman and Argaw Kidane and to direct the live testimony of both witnesses [Docket No. 365]. There is no dispute that Mr. Disman and Dr. Kidane work and live in Maryland, more than 100 miles from the Camden federal courthouse. The Court agrees with Supernus that, under Federal Rule of Civil Procedure 45(c), it cannot mandate the live testimony of these witnesses as they live and work in a different state and over 100 miles from the courthouse. Furthermore, their deposition testimony is admissible under Rule 32(a)(4), which provides that "[a] party may use for any purpose the deposition of a witness, whether or not a party, if the court finds: . . . that the witness is more than 100 miles from the place of hearing or trial . . . unless it appears that the witnesses's absence was procured by the party offering the deposition." In any event, it is hard to see how Actavis suffered any unfair prejudice by the introduction of this deposition testimony at trial. Actavis noticed and took the depositions and had ample opportunity to examine the witnesses.

tablet matrix. Specifically, he testified that the uniformity testing performed by Supernus "show[s] that the matrix of the product that we have is -- has that homogeneous matrix." Tr. 461:14-17 (Kidane Depo).

Similarly, it is undisputed that Oxtellar XR® contains oxcarbazepine. SF p. 6 ¶ 3. Likewise, Oxtellar XR® contains several matrix-forming polymers as described in element 1(b) of Claim 1 in the form of silicified microcrystalline cellulose ("SMCC"), hypromellose (also known as HPMC), and Kollidon 25 (a form of povidone, also known as polyvinyl pyrrolidone or PVP). Tr. 1636:8-12 (Little Direct); PTX 325.1. It also contains agents that enhance the solubility of oxcarbazepine, as described in element 1(c), in the form of sodium lauryl sulfate ("SLS"), hypromellose, and povidones. Tr. 1626:16-22 (Little Direct); PTX 325.1. Finally, Oxtellar XR® contains Eudragit L 100-55, which the parties do not dispute is a release promoting agent. Tr. 1637:9-15 (Little Direct); PTX 325.1.

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b) The Actavis ANDA Product

The parties have stipulated that the Actavis Tablets have the following composition:

Composition of Oxcarbazepine Extended-release Tablets, 150 mg, 300 mg and 600 mg

SF pp. 12-13 ¶ 33; PTX 116.6.

Supernus contends that the Actavis Tablets infringe Claim 1 of the '898 Patent and several claims of the '131 Patent that depend upon Claim 1 of the '131 Patent. Actavis concedes that its product contains certain elements of Claim 1, but not all. Specifically, Actavis concedes that its tablets are meant for once-a-day administration for the treatment of seizures. SF p. 11 ¶ 21; PTX 98.4. There is no dispute that Actavis's label and prescribing information state that the Actavis Tablets are to be used to treat seizures. PTX 98.4; Tr. 597:18-598:9 (Requests for Admission).

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Actavis further concedes that its tablets contain element 1(a) oxcarbazepine, element 1(b) matrix-forming polymers in the form of [redacted], and at least one element 1(d) release promoting agent comprising a polymer with pH-dependent solubility in the form of [redacted].[11] SF p. 13 ¶¶ 36-39; PTX 116.6. Actavis, however, disputes the presence of a homogeneous matrix and an agent that enhances the solubility of oxcarbazepine. The Court's infringement analysis shall, therefore, focus on these two elements.

c) Claim 1

(1) Homogeneous Matrix

All of the asserted claims require a pharmaceutical formulation of oxcarbazepine "comprising a homogeneous matrix . . . ." '898 Patent, Claim 1; '131 Patent, Claim 1; '600 Patent, Claim 1. As noted above, the Court construed "homogeneous matrix" to mean a "matrix in which the ingredients or constituents are uniformly dispersed." Docket No. 244. Further, as mentioned, the phrase "homogeneous matrix" was added

[11] The parties dispute whether [redacted], an ingredient found in the Actavis Tablets, satisfies element 1(d). This is not relevant for the infringement analysis regarding the '898 and '131 Patents for reasons discussed herein. It is, however, relevant to the infringement analysis regarding the '600 Patent and will be addressed infra.

to Claim 1 through two consecutive Office Action responses to overcome prior art references that purportedly disclosed element 1(d) release promoting agents in the coating. See PTX 5.205-07, 262-70, 290-300. The term "homogeneous matrix" was added to the claims to distinguish Supernus's invention, which has all four matrix components in the tablet core, from the prior art references containing certain matrix constituents solely in the coating (which the Patent Examiner had viewed to be part of the matrix). The term was not added to describe the degree of uniformity or homogeneity of the Supernus invention. PTX 5.262-70, 295, 298-99.

To carry its burden of proving infringement as to the "homogeneous matrix" limitation, Supernus presented evidence regarding the manufacturing process by which Actavis creates its ANDA product, FDA-required uniformity testing, and chemical imaging. The Court will address each in turn.

Manufacturing Process

The Plaintiff contends that Actavis's manufacturing process proves that its tablets comprise a homogeneous matrix in which the constituents are uniformly dispersed. To support this position, Supernus presented the testimony of several expert witnesses.

As a starting point, the parties, through their experts, agree that "absent a specific objective not to be homogeneous,

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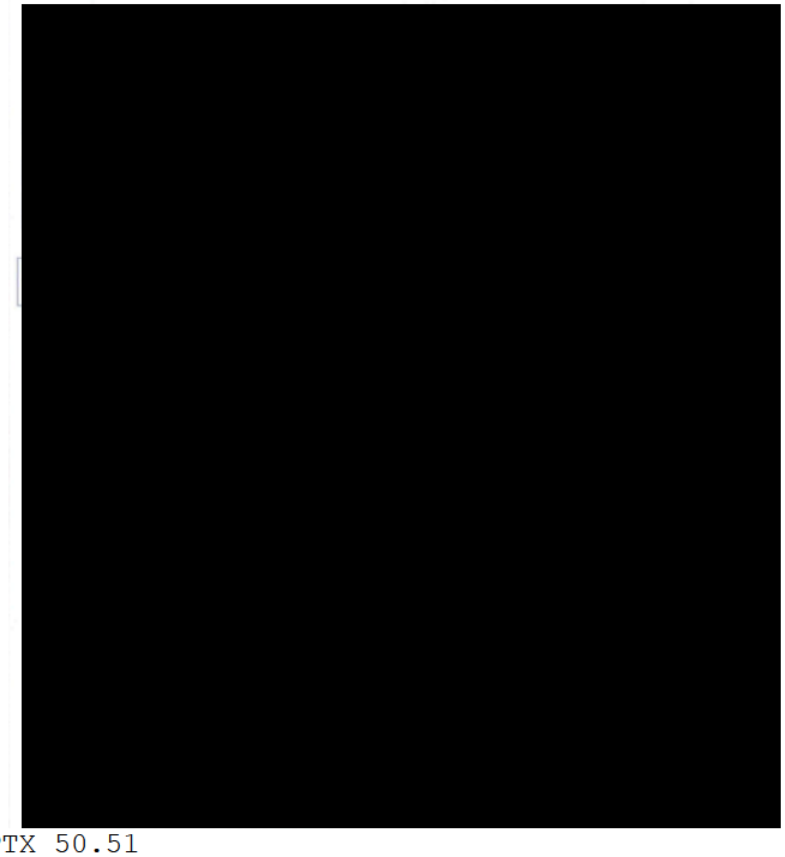
the default objective for a pharmaceutical formulator would be to create a homogeneous matrix formulation that would comprise a uniform dispersion of ingredients[.]" Tr. 1493:12-19 (Hopfenberg Cross); see also Tr. 341:20-23 (Bugay Direct); Tr. 361:13-18 (Bugay Cross). No evidence has been presented that indicates that the Actavis formulators sought to stray from this default objective. In fact, Actavis's manufacturing process establishes that its tablets comprise a homogeneous matrix.

Actavis's manufacturing process involves several steps. The manufacturing as set forth in Actavis's Quality Overall Summary, included in its ANDA, is as follows:



PTX 50.51

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Dr. Little also testified at length regarding Actavis's manufacturing process. The first step, [redacted] Tr. 619:23-620:9 (Little Direct). In its Product Development Report, Actavis claims that [redacted] PTX 42.55.

The second step, [redacted] Tr. 620:10-17. The purpose of [redacted] Id. at 620:15-17; PTX 50.57. In the third step, [redacted] PTX 42.55; Tr. 620:18-621:4 (Little Direct).

The fourth step, [redacted] Tr. 621:5-14 (Little Direct). Actavis discloses in its ANDA that this [redacted]

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[redacted] PTX 42.75.

Dr. Fernando Muzzio, Actavis's expert in chemical imaging, countered that Actavis's manufacturing process results in a non-homogeneous matrix because of [redacted], which is, according to him, "universally used by formulators everywhere to promote uniform homogeneous granulation." Tr. 929:17-23 (Muzzio Direct). He also stated that Actavis's granulation process results in "relatively large granules . . . And because the granules are relatively large, they could not appear everywhere in the tablet in the same proportion." Id. at 929:23-930:9. In Dr. Muzzio's opinion, this results in a non-homogeneous matrix in the Actavis Tablets. When asked by the Court whether homogeneity is simply a product of the type of blender used, Dr. Muzzio responded that "[t]hat's close to one of the concepts I'm using." Tr. 967:5-11 (Muzzio Cross). Actavis's granulation process [redacted] as compared to Supernus's process, which, according to Dr. Muzzio, results in a lower "level of intermingling of ingredients . . . [and] granules that are more diverse." Id. at 967:12-19.

Given Actavis's own description of the purpose of each step in its manufacturing process, the Court gives these opinions little weight. See, e.g., PTX 42.55 ([redacted]); PTX 42.75 ([redacted]

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[redacted]). Furthermore, the Patents-in-Suit clearly contemplated the formation of granules and did not view the fact that certain ingredients were added after the formation of granules to be an impediment to the creation of a homogeneous matrix. See, e.g., '898 Patent, col. 5, ll. 1-9; col. 5, l. 22; Tr. 956:7-958:5 (Muzzio Cross).

The final step [redacted] Dr. Little persuasively testified that the homogeneity achieved in the blend by the previous steps is carried over to the compressed tablet. Tr. 621:25-622:3 (Little Direct). In fact, in Dr. Little's expert opinion, the manufacturing process followed by Actavis in formulating its ANDA tablets results in a homogeneous matrix in those tablets. Id.

Dr. David Bugay, Supernus's expert who is a physical analytical chemist who specializes in spectroscopy, too reviewed Actavis's manufacturing process as set forth in its ANDA. The manufacturing process confirmed his conclusion that the constituents are uniformly dispersed in the Actavis Tablets such that the tablet comprises a homogeneous matrix. Tr. 351:12-20 (Bugay Direct).[12] What's more, the inventors of the Patents-in-

[12] Even Dr. Irwin Jacobs, Actavis's former expert that it has since abandoned, characterized the Actavis ANDA product as "a

Suit stated during prosecution history that "[o]ne of ordinary skill in the art would appreciate that the formulations derived according to the [manufacturing] protocol set forth in the Examples would necessarily comprise a homogeneous matrix." PTX 5.298. Example 4 in the '898 Patent sets forth a manufacturing process that involves blending and high shear granulation prior to tableting. '898 Patent, col. 10, ll. 35-56. [redacted] See PTX 42.41; Tr. 614:14-22 (Little Direct).

The Court finds that Actavis's manufacturing process results in a homogeneous matrix in its tablets.

FDA Uniformity Testing

Pursuant to FDA regulation, all pharmaceutical formulations must pass a series of uniformity tests, including blend uniformity, content uniformity, and dissolution testing, prior to being approved. These tests, which the Actavis Tablets have indisputably passed, likewise demonstrate that the Actavis Tablets comprise a homogeneous matrix in which its constituents are uniformly dispersed.

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homogeneous matrix" after reviewing Actavis's manufacturing process. Tr. 429:11-24 (Jacobs Depo). The parties dispute the admissibility of Dr. Jacobs's testimony at trial. The Court does not rely on any testimony of Dr. Jacobs in reaching its conclusions and, therefore, need not reach the issue of its admissibility.

The FDA requires that blend uniformity testing be performed on all pharmaceutical formulations to ensure the adequacy of mixing. Prior to receiving FDA approval, all pharmaceutical formulations must pass blend uniformity testing. Blend uniformity testing assesses the uniformity of all blended ingredients prior to tableting. It tests "the adequacy of the mixing" by testing various samples from the blend to "determine whether or not [the] product is uniformly dispersed." Tr. 627:5-13 (Little Direct).

Dr. Jack Chen, Actavis's director of analytical chemistry and its 30(b)(6) witness on homogeneity testing, explained the underlying purpose of the uniformity tests mandated by the FDA:

> Q. What is the purpose of running [blend uniformity testing]?
>
> A. It's required by regulation.
>
> Q. Okay. But what is the purpose underlying the regulation?
>
> A. To see how your blend, whether it's homogeneous or not.
>
> Q. Okay. And a positive result or an in-specification result for blend uniformity would indicate that your product is homogeneous?
>
> A. Correct.

Tr. 794:8-13 (Chen Depo) (emphasis added).

Dr. Little also testified that blend uniformity testing tests whether the constituents of the product are "uniformly

dispersed." Tr. 627:5-21 (Little Direct). He further explained that "there's an understanding that if this is blended properly . . . that what you would have is you would have a uniform final product." Id.

Dr. Muzzio testified that the homogeneity of the blend is irrelevant to the term "homogeneous matrix" as construed by the Court because the blend is not a matrix and because blend uniformity testing does not address the spatial distribution of ingredients within the final tablet. Tr. 936:20-937:1 (Muzzio Direct). These arguments miss the point. Although blend uniformity tests examine only the blend, not the final tablet, the Court is persuaded by Dr. Little's expert opinion that if the constituents are properly blended, the final product will necessarily be uniform. Tr. 627:14-21 (Little Direct).

This is likewise true even though blend uniformity testing only directly measures the active ingredient in the blend, here, oxcarbazepine. Once the uniformity of the active ingredient is established, a person of skill in the art would assume that all the other constituents of the blend are also uniformly dispersed. Tr. 630:16-631:4 (Little Direct); Tr. 729:21-731:1 (Little Redirect).[13] The uniformity of the active ingredient is

[13] Dr. Muzzio, Actavis's expert, agreed that a person of ordinary skill in the art generally assumes the uniform dispersion of the excipients once it has been established that the active ingredient is uniformly dispersed. He, however, takes issue

necessarily impacted by the uniformity of the excipients. In Dr. Little's opinion, excipients that are not uniformly dispersed would result in a non-uniform distribution of the active ingredient. Id. at 730:7-731:1.

It is undisputed that the Actavis ANDA product passed blend uniformity testing. PTX 170.3; PTX 572.3. Dr. Little reviewed the results of blend uniformity testing as found in the Actavis ANDA and concluded that the Actavis Tablets are uniform. Tr. 630:2-14 (Little Direct).

In addition to blend uniformity testing, the FDA also requires content uniformity testing. Content uniformity testing, also known as unit dose uniformity testing, is conducted after the blend has been compressed into tablets. This test measures the active ingredient in the final tablet in order to ensure that the same amount of the active ingredient is present across tablets. Tr. 631:11-632:14 (Little Direct). Dr. Little explained that in measuring the active ingredient in each tablet, content uniformity testing also necessarily measures the quality of mixing in, as well as the homogeneity and uniformity

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with this assumption. See Tr. 1057:22-1059:19 (Muzzio Cross). Whether or not Dr. Muzzio's concerns are valid, they do not change the fact that this is the methodology widely used by those skilled in the art. The Court must use the perspective of a person of ordinary skill in the art.

of the final tablet. Id. at 632:1-9.[14] As with blend uniformity testing, the uniform dispersion of the excipients is assumed once the uniformity of the active ingredient is established. Id. Dr. Little cogently explained that if the excipients were not uniformly dispersed, there would be localization of all constituents, including the active ingredient. Id. An in-specification result for content uniformity testing establishes that there is no localization of the active ingredient and, therefore, also no localization of the excipients.

The Actavis Tablets passed content uniformity testing. PTX 50.62; PTX 116.27. The results of the content uniformity testing are consistent with Actavis's manufacturing process and confirm that the Actavis Tablets comprise a homogeneous matrix. Tr. 634:14-635:3 (Little Direct).

Actavis additionally performed ***in vitro*** dissolution tests on its tablets for submission to the FDA. Actavis tested twelve tablets from each strength of its tablets. PTX 39.8, 20, 32; Tr. 635:22-637:16 (Little Direct). Supernus contends that the

[14] Dr. Muzzio, Actavis's expert, actually agrees. Just last year, in an article entitled The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Blends, Dr. Muzzio explained that "In-process dosage unit analysis . . . is an accurate and reflective measure of homogeneity of the product. . . . It accounts for potential segregation after blending. . . . In general, content uniformity of the final dosage form is dependent on the homogeneity of the powder mixture in the blender." Tr. 1049:17-1051:6 (Muzzio Cross).

results of the dissolution tests likewise confirm that the Actavis Tablets comprise a homogeneous matrix. The Court agrees.

Dr. Little explained that dissolution testing "measure[es] how the dosage unit performs. So if the dosage unit is uniformly dispersed, what will happen is, is that the dosage form will behave the same from tablet to tablet to tablet. So you're measuring [the] release profile for a specific tablet in this case. So if everything is blended up appropriately, you would expect it to perform uniformly from tablet to tablet to tablet. If there's heterogeneities [sic] in the system, you would imagine that something would fall apart odd or funny, so you would get a different release profile." Tr. 635:11-21 (Little Direct); see also Tr. 447:13-448:1 (Disman Depo). Dr. Kidane, one of the inventors of the Supernus Patents, also testified in his deposition that "[i]f there is inhomogeneity there would be variability in the dissolution profiles." Tr. 462:1-8 (Kidane Depo).

The results of Actavis's dissolution tests show low variability between tablets, which indicates that the Actavis Tablets "perform uniformly from tablet to tablet," as described by Dr. Little. Tr. 635:17-19 (Little Direct); PTX 39.8, 20, 32. Although the tablet is ultimately "destroyed," in the sense that it dissolves, during dissolution testing, see Tr. 716:12-20

(Little Cross), the Court is persuaded by Dr. Little's expert testimony that dissolution testing functions essentially as a proxy for tablet homogeneity by demonstrating that the tablets perform consistently with each other. See, e.g., Tr. 637:7-16 (Little Direct).

Finally, the Court finds that the results of the FDA-required uniformity testing confirm that Actavis's manufacturing process results in a uniform dispersion of ingredients and establish that the Actavis Tablets comprise a homogeneous matrix.

Chemical Imaging

In further support of its position that the Actavis Tablets comprise a homogeneous matrix, Supernus put forth evidence of chemical imaging of the Actavis Tablets.[15] Dr. Bugay testified at length regarding the Raman imaging tests he performed on the Actavis Tablets as well as the Oxtellar XR® tablets and his conclusions regarding the presence of a homogeneous matrix. Dr. Bugay explained that he was asked by the Plaintiff to examine the Actavis Tablets and the Oxtellar XR® tablets using Raman imaging to determine whether the pharmaceutical formulations of

[15] Supernus contends that the chemical images are "not necessary to show that Actavis's Tablets contain a homogeneous matrix," but that they are consistent with and confirm the other evidence demonstrating that the Actavis Tablets comprise a homogeneous matrix. Pl. Br. at 12. The Court agrees.

each of the tablets comprises a homogeneous matrix, as construed by the Court. Tr. 318:24-320:9 (Bugay Direct).

The first step of Dr. Bugay's analysis required microtomy of the tablets, which entails shaving the tablet samples to expose the interior of the tablets for analysis. Id. at 320:17-321:12. Dr. Bugay then performed Raman spectroscopy to determine what molecular compounds are present in the samples. This process results in a distinct Raman spectrum for each molecular compound that is present. Dr. Bugay testified that each compound's Raman spectrum is like a "unique fingerprint" that allows the experimenter to identify each individual constituent in a tablet sample and whether a particular area contains one or more of the constituents. Id. at 321:13-326:4.

This procedure was repeated for 35,000 data points on each tablet, covering roughly 70% of the tablet's surface. Id. at 326:5-13, 331:1-18. Dr. Bugay persuasively testified that it is crucial to examine as much of the tablet as possible in order to assess the homogeneity of the tablet matrix. Indeed, Dr. Bugay echoed Dr. Little's concern, supra, regarding the size of the tablet examined. On the other hand, Dr. Muzzio only examined 7-8% of the tablet surface. Tr. 396:12-20 (Bugay Cross). Scale is critically important in this analysis, as Dr. Muzzio readily admits. See Tr. 894:20-895:2 (Muzzio Direct) ("And so, for example, if I want to answer the question, is my batch uniform,

or is my blend uniform, then I'm going to use my blend to make tablets, so I have to use samples that are roughly the size of tablets, because the relevant scale at which I have to examine that blend is the tablets, because that's what I'm going to make with that blend. I'm going to make tablets. So that's the right scale of examination."); Tr. 964:7-25 (Muzzio Cross) (". . . there is always this issue of at which scale you're examining the structure . . . If you go down to atoms, nothing is homogeneous. . . . Well, what I said is that when you look to that scale, it would always look heterogeneous, right?"). Given the material importance of scale, the Court is persuaded that Dr. Bugay's chemical images, which examine the vast majority of the tablet surface, more accurately assess the homogeneity of the matrix.[16]

[16] Dr. Bugay's comparison of the chemical images to images of a person's head is likewise persuasive and helpful to this Court's assessment of the competing chemical images. In explaining that scale and perspective is crucial to this analysis, he gave the following analogy: "If I take a picture looking downward upon your head from a foot above, I see that you have hair and you have a full head of hair. If I bring that camera down to a different perspective to just above your scalp and I take a picture that goes between the hair follicles I would say you are bald. . . . And so without that context you can make this image say one thing or it makes you say another thing. In consideration of that, that's why I did my imaging with respect to as much of the tablet as possible so it's the right perspective that you are looking at as taught by Claim 1 of the patent." Tr. 395:6-23 (Bugay Direct).

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By processing and compiling the thousands of data points, Dr. Bugay created color-coded Raman chemical images which indicate both the presence and the location of the various constituents in the tablet sample. Tr. 339:8-340:13 (Bugay Direct). Dr. Bugay then confirmed this data using extensive validation procedures. Id. at 346:1-349:1.

Raman chemical images of the Actavis Tablets were created that show the presence of oxcarbazepine, [redacted] act as element 1(b) matrix-forming polymers. PTX 253. Supernus argues that [redacted] also serves as an element 1(c) solubility enhancer. Actavis disputes this. [redacted], also known as [redacted] respectively, are element 1(d)s release promoting agent with pH-dependent solubility. [redacted], Supernus posits, is a release promoting agent that is not a polymer with pH-dependent solubility. The parties dispute whether this compound satisfies element 1(d).

Dr. Bugay also prepared Raman chemical images of the Oxtellar XR® tablets that show the presence of oxcarbazepine, MCC, HPMC, SLS, Methacrylic Acid Copolymer Type C, and PVP. PTX 280. The results of Dr. Bugay's Raman imaging on the Actavis Tablets and Oxtellar XR are as follows:

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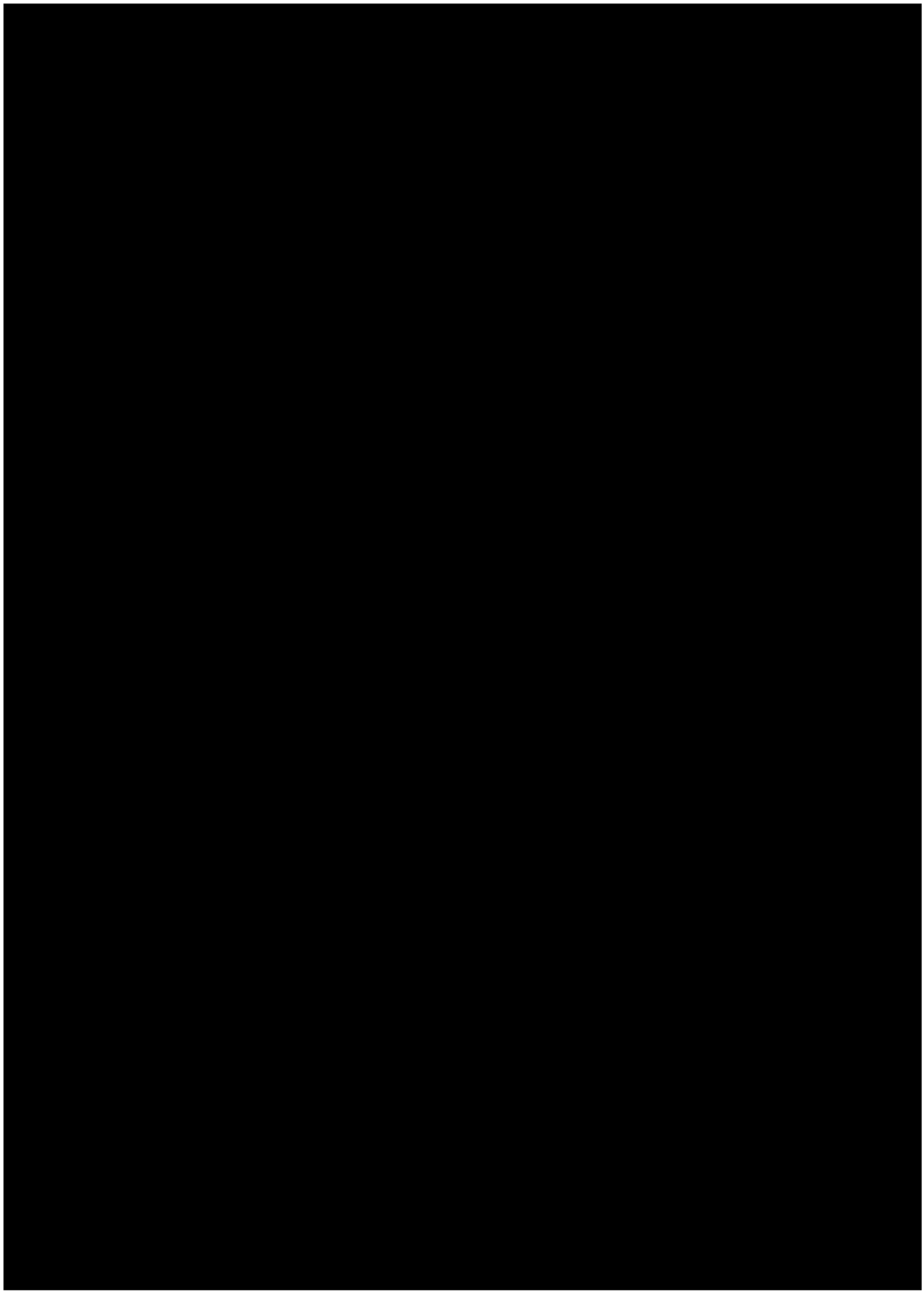

Dr. Bugay visually assessed the Raman chemical images and concluded that each of the constituents in the Actavis ANDA product is uniformly dispersed throughout the tablet and, therefore, that each tablet comprises a homogeneous matrix.[17] Tr. 340:25-342:6 (Bugay Direct). The constituents are not localized in one area alone, but rather are found throughout the tablet surface. While the constituents are admittedly not meticulously arranged in the tablet, Dr. Bugay explained that there are limitations when it comes to molecular compounds. Tr. 341:20-23 (Bugay Direct) ("The objective of formulators in generating or creating a pharmaceutical manufacturing process is to create, okay, a consistent homogeneous product, okay? Do we get it perfect? No. We have limitations in that."). A person of ordinary skill in the art would understand that molecules cannot be perfectly lined up by a formulator the way that bricks

[17] The Defendants insist that Dr. Bugay employed a "quadrant theory" to evaluate the Raman chemical images and determine uniformity. Dr. Bugay denied the use or existence of any such theory and clarified that he used the term "quadrant" only to describe the mental process of visually assessing the images. As part of his visual assessment, he determined whether there was localization of any excipients in a particular quadrant of the image. If there had been such localization, then he would immediately conclude that the excipients were not uniformly dispersed. Since he did not encounter any such localization, he then continued to visually inspect each section of the image in smaller sections to assess uniformity. Tr. 373:23-375:6 (Bugay Cross). The Court agrees with Supernus and Dr. Bugay that there is no "quadrant theory" per se. Dr. Bugay was merely attempting to explain how he visually inspected the images.

can be exactly laid out by a mason. Id. at 341:14-23. This is consistent with Dr. Little's testimony at the Markman hearing, as outlined supra.

In Dr. Bugay's expert opinion, homogeneity in this context is measured by lack of localization. Id. at 341:5-342:6 ("If we go back to the oxcarbazepine image for a minute, as you look at this, I don't see that the active here is localized in one area. . . . I see that the pixels are dispersed throughout the entire image. . . . given my pharmaceutical experience, 30 years of looking at tablets and such, I look at that as being uniformly dispersed."). Dr. Bugay's explanation of how a person of ordinary skill in the art would understand homogeneity and uniformity in this context is illustrative and merits reproduction here in full:

> I look at this in the context of a person skilled in the art of pharmaceutical analysis. Okay? And so we know that we cannot get a perfect uniform distribution, as I mentioned today, like a mason doing a herringbone pattern or doing end-to-end blocks in a brick wall. Okay? Yet we do know we wish to have the constituents dispersed through the tablet. We know that individuals snap a tablet in half and take half in the morning and half in the evening, and we don't want all the API [active pharmaceutical ingredient] to be over in that one half because later in the day they don't get their medication.
>
> And so when we look at this term, it's uniformly dispersed, we look at that knowing that we can't have the perfect brick pattern, yet we do know we want those constituents to be dispersed throughout that tablet matrix, and by the design or the experiments that I did, namely, the preparation, the Raman

> imaging, and then the interpretation and seeing that there wasn't localization here or there, that led to my opinion, in the context of the pharmaceutical manufacturing process and my experience, that it was uniformly dispersed.

Tr. 373:3-22 (Bugay Cross).

Dr. Muzzio agreed in substance with Dr. Bugay's measure of homogeneity. Dr. Muzzio testified that, per the Court's construction of "homogeneous matrix," "you have to have [a] substantially uniform amount of each ingredient in each location of the tablet." Tr. 893:8-17 (Muzzio Direct).

Further, Dr. Little agreed with Dr. Bugay's assessment of the Raman images. He testified that the Raman chemical images of the Actavis Tablets demonstrate that all the constituents are found in all areas of the tablet. None are isolated or segregated in, for example, just the coating or the core of the tablet. Tr. 638:23-639:17 (Little Direct). In his expert opinion, this establishes that each Actavis Tablet comprises a matrix in which all of the constituents are uniformly dispersed.

Defendants make much to do about the fact that Dr. Bugay was unable to create a Raman chemical image demonstrating the presence and location of [redacted] in the Actavis Tablets. See, e.g., Defendants' Post-Trial Brief ("Defs. Br.") at 4 [Docket No. 391]; Tr. 358:7-15, 359:21-361:1 (Bugay Cross). Dr. Bugay testified that he was unable to do so, even though it is undisputed that [redacted] is present in the Actavis Tablets,

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PTX 116.6, due to the low concentration of [redacted] in the Actavis Tablets. Tr. 359:21-361:1 (Bugay Cross). Dr. Bugay explained, however, that it is possible that [redacted] would have been present in larger concentrations in a different cross-section or "slice" of the tablet. Id. at 360:4-361:1; Tr. 351:22-352:15 (Bugay Direct). He likened this to an "iceberg effect," wherein the quantity shown in the image may depend on where on the "iceberg" he sliced. Tr. 344:3-16 (Bugay Direct); Tr. 412:3-18 (Bugay Cross) (". . . when we slice through a tablet, we know for a fact that we don't slice through the equator of every single constituent that's in the tablet."). The fact that the excipients all went through the same manufacturing process, coupled with the data supporting uniform dispersion of the other constituents, allowed Dr. Bugay to conclude that [redacted] is also uniformly dispersed throughout the Actavis Tablet. Tr. 352:17-353:3 (Bugay Direct). The Court finds this explanation credible and persuasive.

Similarly, although Dr. Bugay only tested the 600 mg Actavis Tablets, in his expert opinion, the 150 mg and 600 mg tablets also comprise homogeneous matrices in which all the constituents are uniformly dispersed since each tablet is created through the same manufacturing process. The only

difference is in the amount of each constituent.[18] This does not affect the homogeneity of the tablets. Id. at 353:7-17. Additionally, Dr. Bugay testified that the objective of any formulator creating a standard pharmaceutical formulation is to achieve a homogeneous matrix. Id. at 341:20-22; Tr. 361:13-18 (Bugay Cross).

On cross-examination, Dr. Bugay was presented with the Raman chemical images for both the Actavis Tablet and the Supernus Oxtellar XR® tablet. Dr. Bugay refused to compare the uniformity or homogeneity of the two tablets to each other, correctly noting that the two tablets should not be compared to each other. Rather, the tablets should each be compared to the claims of the relevant patents. Tr. 376:19-377:19 (Bugay Cross). Dr. Bugay's testimony on cross-examination is enlightening:

> In addition, why are we comparing Oxtellar -- excuse me Oxtellar XR® with a different process of producing it than the Actavis product? My understanding of this process is that I looked at determining whether a homogeneous matrix existed, based upon comparing the Actavis product to the elements of Claim 1. Not a comparison test between Actavis versus Supernus's product. It wasn't a comparison test to this -- to this unknown, okay? They are made differently. Their particle sizes are differently [sic]. That means that as they come out of the process, there's [sic] going

[18] This is supported by Actavis's request for an ***in vivo*** bioequivalence waiver from the FDA which states there is "formulation proportionality" and that the data for the 600 mg tablets may be extrapolated to the 150 mg and 300 mg tablets. PTX 97.3.

> to be differences. But what's most important is that as you look at it -- Counsellor, do you see a localization in the bottom image of all the pixels being to the upper right-hand side? No. We see those blue pixels dispersed throughout an entire two-dimensional area. . . . And so because of that, and because we understand we don't have a perfect process, we are trying to achieve it, we see that it is dispersed there.

Id. at 376:19-377:12.

While Actavis is correct that "[o]ur case law does not contain a blanket prohibition against comparing the accused product to a commercial embodiment," Adams, 616 F.3d at 1288, the Court nonetheless finds that Actavis is improperly attempting to limit the term "homogeneous matrix" to what is seen in Oxtellar XR®. The Adams court held that "when a commercial product meets all of the claim limitations, then a comparison to that product may support a finding of infringement." Id. at 1289 (emphasis added). Other Federal Circuit precedent, however, makes clear that a defendant may not prove non-infringement merely by comparing its accused product to a commercial embodiment of the patentee's invention. See, e.g., Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1347 (Fed. Cir. 2003) (vacating finding of non-infringement because "the court eschewed the cardinal principle that the accused device must be compared to the claims rather than to a preferred or commercial embodiment."); Zenith Labs., Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418, 1423 (Fed. Cir. 1994)

("As we have repeatedly said, it is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent."); SDS USA Inc. v. Ken Specialties Inc., 122 F. Supp. 2d 533, 539 (D.N.J. 2000) (collecting cases).

Actavis's expert, Dr. Muzzio, willingly compared what Dr. Bugay would not. He testified that the Raman images of the Actavis Tablet "show[ed] lack of homogeneity" because the oxcarbazepine particles were often "lumped together, agglomerated." Tr. 900:13-25 (Muzzio Direct). The Supernus tablet, on the other hand, "comes much closer, in [his] mind, to what [he] would consider a homogeneous matrix. . . . It seems to have a very close to uniform distribution." Id. at 901:11-15. He formed his conclusions regarding homogeneity not by comparing Actavis's ANDA product to the Patents-in-Suit, but to the commercial embodiment, Oxtellar XR®. See id. at 901:21-902:5 ("Well, in my opinion, again looking at this from the perspective of how I understand the claim construction provided by the court, on the left I see Actavis having a tablet where, as I said, the drug is lumped into agglomerates containing many types of particles each and there's hardly any drug at all and there's a variation as I move from left to right. In comparison I see the Supernus distribution of the drug being very uniform,

probably as close to completely uniform as I would expect something could be where there's drug everywhere."); Tr. 960:2-8 (Muzzio Cross) ("It's [Oxtellar XR®] much more homogeneous by a significant degree than what I see in the Actavis matrix.").

Dr. Muzzio also performed his own Raman imaging to create three dimensional Raman images for the Actavis Tablets and Supernus's Oxtellar XR® tablets. DTX 495. Comparing the three dimensional Raman images for the Actavis and Supernus tablets, he testified that, in the Supernus tablets, "there is a much more intimate distribution of – a much more homogeneous distribution of ingredients. . . . the degree of commingling is much, much more intimate" than in the Actavis Tablets. Tr. 909:9-18 (Muzzio Direct). Dr. Muzzio came to this conclusion from an analysis of merely 1/15th of the Actavis Tablet, compared to Dr. Bugay's analysis of 70-80% of the tablet. Tr. 990:5-991:24 (Muzzio Cross). The cross-examination of Dr. Muzzio effectively demonstrated what Dr. Muzzio had previously explained was critically important, namely the question of scale. See id. at 992:3-993:2. When focusing on solely a 1/15th section of Dr. Bugay's Raman image showing the presence and location of SLS in the Oxtellar XR® tablet, the distribution of SLS seems anything but uniform. Yet, the parties agree that each Oxtellar XR® tablet as a whole comprises a homogeneous matrix comprising, in part, SLS. This is demonstrated by

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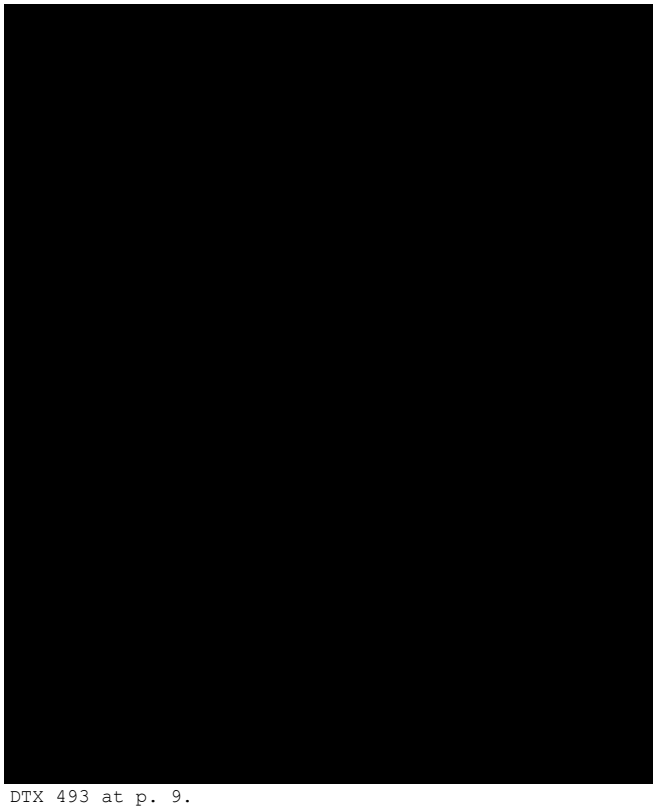
assessing the entirety of Dr. Bugay's Raman image. See PTX 280.12; Tr. 992:3-993:2 (Muzzio Cross).

Similarly, Dr. Muzzio's Near Infrared ("IR") imaging of the Actavis and Supernus tablets shows the presence of oxcarbazepine throughout the tablets. DTX 493. Although the Near IR image of the Actavis Tablet shows areas that have a high concentration of oxcarbazepine and other areas that have a comparatively low concentration of oxcarbazepine, see Tr. 912:17 (Muzzio Direct), Dr. Muzzio conceded that "the two halves don't look very different from each other." Id. at 913:23-24. This, too, confirms that there is no localization of constituents in the Actavis Tablets.



DTX 493 at p. 9.

Although it can be said that the constituents are dispersed "more" uniformly in the Supernus Oxtellar XR® tablets than the Actavis Tablets, this has no bearing on whether the Actavis Tablets comprise a homogeneous matrix. In fact, despite making these comparisons, Dr. Muzzio admits that "there are degrees of homogeneity." Tr. 904:11 (Muzzio Direct).[19] Thus, the Court finds that the chemical imaging confirms that both tablets comprise a homogeneous matrix, even if, when compared to each other, the dispersion of the constituents may be considered more uniform in one than the other.[20] It is irrelevant whether the Actavis Tablets are "less homogeneous" than the Oxtellar XR® tablets.[21] In sum, the Court holds that the Actavis Tablets

[19] Dr. Muzzio's testimony in comparing the Near IR images illuminates the fact that homogeneity exists in degrees. Tr. 914:19-24 (Muzzio Direct).

[20] Although the Defendants urge the Court to rely primarily on the chemical images to establish that the Actavis Tablets do not comprise a homogeneous matrix, the Court, like Dr. Muzzio, "hesitate[s] to put too much emphasis just on pictures," Tr. 1043:1-2 (Muzzio Cross), and does not. See supra footnote 14.

[21] This point was made all the more clear when the parties began quibbling over whether a matrix is "very" or "quite" homogeneous. See Tr. 962:14-23 ("Q. Now you, yourself, acknowledge, do you not, that the Supernus product is very homogeneous? A. I think that the matrix in the Supernus tablets is quite homogeneous, yes. Q. Well, my question is, haven't you – haven't you given the opinion that the Supernus tablets are very homogeneous? A. There's a difference between "quite" and "very"?"), 964:2-6 ("Q. So earlier, you said it's most homogeneous, it's more homogeneous, it's closer – it's practically close to what – I don't know, what's perfect or something, but what is it? Is it very homogeneous or is it just more homogeneous than Actavis?") (Muzzio Cross).

comprise a homogeneous matrix, as construed by this Court and as understood by a person of ordinary skill in the art.

(2) Agent that Enhances the Solubility of Oxcarbazepine

Supernus contends that two compounds in the Actavis ANDA tablets satisfy element 1(c) of Claim 1, which requires "at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents." '898 Patent, Claim 1(c). According to the Plaintiff, two excipients in the Actavis ANDA tablets, [redacted] and [redacted] (also known as [redacted]), the particular grade of HPMC in the Actavis Tablets, constitute agents that enhance the solubility of oxcarbazepine.[22] See,

[22] Supernus also moved in limine to preclude Actavis from arguing that its ANDA tablets lack an element 1(c) agent that enhances the solubility of oxcarbazepine because this position was not disclosed by Actavis in its non-infringement contentions as required by Local Patent Rule 3.6(e) [Docket No. 327]. The Court denied the motion without prejudice [Docket No. 355]. The motion was renewed by Plaintiff at trial. The Court holds that there was no prejudice or surprise to Supernus, given that Supernus was aware of Actavis's position since, at the very latest, February 9, 2015 when Actavis denied its admission request regarding the presence of an element 1(c) agent that enhances the solubility of oxcarbazepine. Furthermore, Supernus has pursued and engaged in discovery on this claim element since late 2013. Given the centrality of element 1(c) in the parties' discovery and motion practice, as well as the litigation as a whole, the Court denies the Plaintiff's motion, once again, with prejudice.

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e.g., Tr. 642:14-644:2 (Little Direct); Tr. 293:15-22 (Chyall Direct). The Court will address [redacted] first.

Dr. Leonard Chyall, Supernus's expert in analytical testing of pharmaceutical compositions, performed solubility tests on oxcarbazepine in the presence of [redacted]. Tr. 282:20-287:2 (Chyall Direct). He did not, however, run any solubility or dissolution tests on the Actavis Tablets themselves. Tr. 297:1-8 (Chyall Cross).

In performing the solubility tests, Dr. Chyall first prepared four solutions with varying percent concentrations of [redacted] to test what solubility enhancing effect, if any, [redacted] has on oxcarbazepine. The four solutions contained 0% [redacted] (control), 1% [redacted], 5% [redacted], and 10% [redacted]. After placing oxcarbazepine in the various [redacted] solutions and agitating the materials overnight, Dr. Chyall used a high pressure liquid chromatography ("HPLC") test to measure how much oxcarbazepine dissolved in the solution. Tr. 283:13-284:2, 285:6-287:2 (Chyall Direct). Dr. Chyall's testing presented the following results:

[redacted]

PTX 285.1.

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The results of Dr. Chyall's HPLC tests indicate that as the concentration of [redacted] increases, so does the solubility of oxcarbazepine. Tr. 292:20-293:22 (Chyall Direct). Dr. Chyall persuasively testified that [redacted] is an agent that enhances the solubility of oxcarbazepine, as required in element 1(c) of Claim 1. Id.

Dr. Little, relying in part on Dr. Chyall's solubility testing, also concluded [redacted] acts in the Actavis Tablets as an agent that enhances the solubility of oxcarbazepine. He also relied upon the relevant patent claims and specifications, the patent prosecution history, peer-reviewed literature, product literature for [redacted], and Actavis's manufacturing process and batch records to come to this conclusion. Tr. 643:8-14, 651:2-20 (Little Direct).

A reading of the patent specifications supports this conclusion. The specifications for the '898 Patent state that the "[s]olubilizers preferred in this invention include . . . complexing agents such as low molecular weight polyvinyl pyrrolidone [PVP] . . ." '898 Patent, col. 5, ll. 9-15. The Supernus Patents clearly contemplate PVP, the generic term for Kollidon, as a solubilizer. The fact that the "preferred" solubilizer is a low molecular form of Kollidon is of no moment. Nothing in the patent or its specifications limits the solubilizers to these "preferred" types. See, e.g., Tr. 645:6-

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20 (Little Direct). In fact, Dr. Little testified that the molecular weight does not impact the ability of the compound to create a complex, as required by the Patents-in-Suit. Id. He further testified that "low molecular weight" is a relative term. While he would not necessarily characterize [redacted] as a low molecular weight PVP, there are PVP grades with much higher molecular weight than [redacted]. Tr. 689:13-17 (Little Cross).

Moreover, in addressing the prior art, the Patent Examiner identified another patent which disclosed a pharmaceutical formulation comprising several constituents, including polyvinyl pyrrolidone. PTX 5.385. After polyvinyl pyrrolidone, the patent examiner added a note in parentheses: "(a surface acting agent; at least one agent that enhances the solubility of oxcarbazepine; that polyvinylpyrrolidone is known in the art as a surface active agent, . . .)." Id.

Even the product brochure issued by BASF, the company that supplies Actavis with its [redacted], states that [redacted] "can also be deployed to modify the viscosity of liquid dosage forms and improve the bioavailability of certain poorly soluble actives." PTX 306.6; Tr. 650:5-20 (Little Direct). Likewise, the Handbook of Pharmaceutical Excipients, relied upon by Dr. Little, explains that "Povidone is used as a solubilizer . . . and has been shown to enhance dissolution of poorly soluble

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drugs from solid-dosage forms." PTX 292.22; Tr. 651:21-653:3 (Little Direct). It is well-established that oxcarbazepine is a poorly soluble active ingredient. See, e.g., Tr. 650:12-14 (Little Direct); Tr. 61:1-7 (Bhatt Direct). Dr. Little testified that both the [redacted] brochure and the Handbook of Pharmaceutical Excipients are consistent with his conclusion that [redacted] enhances the solubility of oxcarbazepine. Tr. 650:15-20 (Little Direct).

While the Defendants insist that [redacted] is merely a "binder" and not an agent that enhances the solubility of oxcarbazepine, the functions listed in Actavis's ANDA are merely proposed functions and a single compound may have several functions. See, e.g., Tr. 606:4-16 (Little Direct). The Court agrees with the Plaintiff's position that just because "Actavis is smart enough not to say we have a solubility enhancer in the form of PVP" does not mean that it is not in practice a surface active agent that enhances the solubility of oxcarbazepine. Tr. 861:15-21. Dr. Little persuasively explained this.

To prove that there is no solubility enhancing agent in its ANDA tablets, the Defendants also rely on a letter from the FDA to Actavis in response to Actavis's bioequivalence study report, which reads: [redacted]

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[redacted] PTX 54.4.

Yet, rather than address [redacted], as the FDA requested, [redacted] PTX 41.8. Dr. Harold Hopfenberg, Actavis's expert witness, testified and the Court agrees that this [redacted] must be a reference to [redacted] since that is the only [redacted] listed in the chart in Actavis's ANDA outlining the composition of its generic tablets. Tr. 1483:2-15 (Hopfenberg Cross). Dr. Hopfenberg further testified that increasing the wettability of an active ingredient by reducing the contact angle is one way in which a surface active agent works. Id. at 1484:13-17; see also Tr. 1475:8-10 (Hopfenberg Cross); PTX 235.3 (defining surface active agent and noting that "there are three categories of surface active agents: detergents, wetting agents, and emulsifiers) (emphasis added). The Court observes that element 1(c) of the Supernus Patents requires "at least one agent that enhances the solubility of oxcarbazepine selected from the group

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consisting of surface active agents" and others. '898 Patent, col. 12, ll. 60-63.

Given the extensive expert testimony from Dr. Little and Dr. Chyall, Dr. Chyall's solubility testing, and the scientific literature available, the Court concludes that [redacted] acts as an agent that enhances the solubility of oxcarbazepine in the Actavis Tablets. The Actavis Tablets, therefore, comprise an element 1(c) solubility enhancing agent in the form of [redacted]

The Court does not agree with the Defendants' argument that the "examples in the specification also directly support the conclusion that HPMC and PVP are not solubility enhancers." Defs. Br. at 14 (emphasis in original). Table 1 recites the composition of three "non-enhanced" oxcarbazepine formulations that contain "no solubility/release enhancer." '898 Patent, col. 2, ll. 60-62, col. 9, ll. 11-37. Only the CR-M formulation contains [redacted] and only the CR-S formulation contains [redacted]. None of the non-enhanced formulations contain a release promoter. Table 4 lists the composition of one enhanced and one non-enhanced oxcarbazepine formulation. Id. at col. 10, l. 56-col. 11, l. 15. The non-enhanced formulation is described in the Supernus Patents as one "without solubility enhancer." Id. at col. 3, ll. 14-17. [redacted] is not present in either of the formulations in Table 4. [redacted] is present in

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both. Notably, however, [redacted], a release promoter, is only present in the enhanced formulation.

The Supernus Patents clearly state that a "combination of solubility and release promoters is contemplated in this invention." Id. at col. 4, ll. 14-17. The description of Table 1 states that the non-enhanced formulations contain no "solubility/release enhancer," referring, in this Court's opinion, to the combination of solubility and release promoters required in the invention. This is confirmed by Dr. Bhatt's testimony that solubility enhancing agents alone were insufficient and that a release promoter was also required. Tr. 75:11-17 (Bhatt Direct) (". . . the tablets needed more porosity to allow the fluid, the media, to go into the tablet and dissolve or help dissolve the drug along with the solubility enhancer.").

Likewise, the non-enhanced formulation in Table 4 does not contain a combination of solubility enhancing and release promoting agents, while the enhanced formulation has both. To the extent that the description of the non-enhanced formulation in Table 4 is not referring to the combination of solubility and release promoters, the Court still finds it irrelevant to its analysis of whether [redacted] satisfies claim element 1(c) as it is not present in either of the formulations in Table 4. The Plaintiff is correct that "the patents never expressly describe

a [redacted]-containing formulation as 'without solubility enhancer.'" Plaintiff's Responsive Post-Trial Brief ("Pl. Resp. Br.") at 13 [Docket No. 408].

Supernus claims that, in addition to [redacted], [redacted] also acts as an element 1(c) solubility enhancing agent in the Actavis Tablets. The Court, however, disagrees and finds that Supernus has not established by a preponderance of the evidence that [redacted] is an agent that enhances the solubility of oxcarbazepine, such that it satisfies claim element 1(c) of the Supernus Patents.

Dr. Chyall was unable to run comparable solubility tests on [redacted]. He testified that [redacted] is not amenable to the solubility testing he performed because the highest [redacted] concentration solution that he could achieve was 1%. Tr. 287:3-19 (Chyall Direct). While he was able to run solubility tests using solutions with very low concentrations of [redacted] all below 1%, Dr. Chyall concluded that the solubility enhancing differences between the varying concentrations amounted to experimental error. Id. at 287:13-19; Tr. 298:21-299:5 (Chyall Cross). Dr. Chyall reached no conclusions about the solubility enhancing effect of [redacted] on oxcarbazepine. Tr. 298:5-6 (Chyall Cross).

Dr. Little, however, concluded, after reviewing peer-reviewed literature, product literature for [redacted], and

Dr. Bugay's Raman chemical images, that [redacted] is an agent that enhances the solubility of oxcarbazepine. See, e.g., Tr. 653:4-7 (Little Direct). As with [redacted], the specifications identify "low molecular weight hydroxypropl methyl cellulose [HPMC]" as a preferred solubilizer. '898 Patent, col. 5, ll. 9-16. Nothing in the Patents-in-Suit or the specifications limits the solubilizing agent to the non-exhaustive listed of "preferred" solubilizers.

The [redacted] brochure issued by Dow, the company which supplies Actavis with its [redacted] for use in its generic tablets, explains that "Methocel products act as surfactants," which are also known as surface active agents. PTX 309.5; Tr. 655:1-11 (Little Direct). It is well-established in the peer-reviewed literature that "HPMC possesses surface active properties." PTX 294.3; Tr. 655:18-656:3 (Little Direct). Another peer-reviewed article states that HPMC "possesses a significant solubilizing effect which is due to the formation of a water soluble drug-polymer complex." PTX 295.2; Tr. 654:5-10 (Little Direct). However, this article discussed a different active ingredient called piroxicam. Id. While this article may establish that HPMC is an agent that enhances the solubility of piroxicam, it tells the Court nothing with regard to whether it has the same solubilizing effect on oxcarbazepine.

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Dr. Little testified that the literature he reviewed about HPMC was consistent with his understanding, based on his years of experience as chemical engineer, that [redacted] is a surface active agent. Tr. 656:2-3 (Little Direct). Dr. Little also concluded that [redacted] can also act as a hydration promoting agent, as described in element 1(c) of Claim 1. HPMC is a hydrophilic compound that draws water into a formulation, causing the formulation to swell dramatically. Id. at 656:4-13. Dr. Little testified that Dr. Bugay's Raman chemical images, showing that HPMC and oxcarbazepine are co-located in the Actavis Tablets, confirm this conclusion. Id. at 656:14-657:4; PTX 253.17. This co-location of HPMC and oxcarbazepine in the Raman images of the Actavis Tablets is the only evidence that relates to [redacted] impact on oxcarbazepine.

Although the expert testimony and the scientific literature suggests that [redacted] may enhance the solubility of certain compounds, there is insufficient evidence in the record to establish by a preponderance of the evidence that [redacted] enhances the solubility of oxcarbazepine. In fact, Dr. Hopfenberg testified that he "found nothing in the literature . . . that demonstrated that there was an affect [sic] of solubilization provided by [redacted], the specific grade [in the Actavis Tablets] and oxcarbazepine. I've seen no experiments that would be consistent with the conclusion that [redacted]

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would solubilize oxcarbazepine." Tr. 1363:3-9 (Hopfenberg Direct). Furthermore, Dr. Chyall's solubility tests, which demonstrated that [redacted] enhances the solubility of oxcarbazepine, were inconclusive with regards to [redacted].

Dr. Bhatt explained that explained that excipient compatibility studies are essential because "[e]very drug molecule is unique in its own right. Just because we have used component A in a previous drug product does not guarantee that that component is going to be acceptable in a project that's using drug B." Tr. 71:24-72:3 (Bhatt Direct). As Dr. Bhatt astutely observed, "[o]xcarbazepine . . . is a chemical with its own properties. It has its own physical properties, and it behooves us as good scientists to study even standard excipients to ensure that those standard, quote/unquote, standard excipients are going to be compatible with the drug at hand, which is oxcarbazepine." Id. at 72:4-9.

Element 1(c) of Claim 1 specifically calls for an agent that enhances the solubility of oxcarbazepine. Given the lack of evidence regarding the solubility enhancing effect of [redacted] on oxcarbazepine, this Court will not consider [redacted] as satisfying element 1(c) of Claim 1 of the '898 Patent.

In sum, the Court holds that the Actavis Tablets infringe Claim 1 of the '898 Patent and Claim 1 of the '131 Patent.

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Actavis's ANDA product is admittedly a pharmaceutical formulation for once-a-day administration of oxcarbazepine for the treatment of seizures. This Court has found that Actavis's ANDA product additionally comprises a homogeneous matrix comprising oxcarbazepine (element 1(a)), [redacted] (element 1(b)), [redacted] (element 1(c)), and [redacted] (element 1(d)).

d) The Dependent Claims

Having established that the Actavis Tablets infringe Claim 1 of the '898 and '131 Patents, the Court now turns to the dependent claims. See Monsanto Co. v. Syngenta Seeds, Inc., 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting Wahpeton Canvas Co., Inc. v. Frontier, Inc., 870 F.2d 1546, 1552 n. 9 (Fed. Cir. 1989) ("One may infringe an independent claim and not infringe a claim dependent on that claim.").

(1) The Pharmacokinetic Claims of the '898 and '131 Patents

Claims 6, 7, and 8 of the '898 and '131 Patents were evaluated at trial as a group called the pharmacokinetic or "PK" claims. Claim 6 and 7 depend upon Claim 1 and Claim 8 depends upon Claim 7.

The PK Claims of the '898 Patent read:

> 6. The pharmaceutical formulation of claim 1, wherein the amount of oxcarbazepine is effective to produce a

> steady state blood level of monohydroxy derivative of oxcarbazepine in the range of about 2 µg/ml to about 10 µg/ml.
>
> 7. The pharmaceutical formulation of claim 1, wherein the formulation is effective in minimizing fluctuations between C_{min} and C_{max} of monohydroxy derivative of oxcarbazepine.
>
> 8. The pharmaceutical formulation of claim 7, which provides C_{max} levels of monohydroxy derivative of oxcarbazepine in the range of about 6 µg/ml to about 10 µg/ml and C_{min} levels of monohydroxy derivative of oxcarbazepine in the range of about 2 µg/ml to about 5 µg/ml.

The PK Claims of the '131 Patent are nearly identical and read:

> 6. The method of claim 1, wherein the amount of oxcarbazepine is effective to produce a steady state blood level of monohydroxy derivative of oxcarbazepine in the range of about 2 µg/ml to about 10 µg/ml.
>
> 7. The method of claim 1, wherein the formulation is effective in minimizing fluctuations between C_{min} and C_{max} of monohydroxy derivative of oxcarbazepine.
>
> 8. The method of claim 7, which provides C_{max} levels of monohydroxy derivative of oxcarbazepine in the range of about 6 µg/ml to about 10 µg/ml and C_{min} levels of monohydroxy derivative of oxcarbazepine in the range of about 2 µg/ml to about 5 µg/ml.

Supernus retained Dr. Dhiren Thakker, a pharmacokinetics and pharmacodynamics expert, to compare the pharmacokinetics of the Actavis Tablets to the limitations of the PK Claims. To do so, Dr. Thakker used the MHD blood levels data for the 600 mg tablets included in the bioequivalence study report submitted by Actavis to the FDA. Tr. 532:5-533:8 (Thakker Direct); PTX 104. This data simply reflected the MHD levels over time in the

subjects after one dose of the Actavis ANDA product. Tr. 533:1-11 (Thakker Direct). He then used a superposition analysis to project what the MHD blood levels would be after multiple dosages. This involved adding an additional curve at every dosage interval, i.e. since the Actavis Tablets are for once daily administration, an additional curve was added every twenty-four hours. Id. at 533:12-535:3. By continuing to add curve until C_{min} and C_{max} stabilized, Dr. Thakker was able to determine steady state blood level. Id. Dr. Thakker credibly testified that this is a well-established method and common industry practice used to calculate and project plasma levels for multiple dosing of various products. Id. Actavis's expert in pharmaceutical sciences, Dr. Michael Mayersohn, likewise utilized this methodology. See Tr. 1075:12-16, 1081:14-24 (Mayersohn Direct).

The Defendants attempt to discredit Dr. Thakker because he was only able to calculate the steady state blood levels for thirty-six of the forty-one subjects in Actavis's study. Tr. 553:25-559:2 (Thakker Cross). Dr. Thakker explained that there was insufficient data available to calculate the terminal elimination rate constant, which is a necessary figure for conducting a superposition analysis. Tr. 537:20-538:22 (Thakker Direct). Dr. Thakker had no concerns about this. Id. at 538:23-539:3. Further, it appears that Actavis similarly had no

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concerns about the insufficient test data for these five subjects. In its bioequivalence study report submitted to the FDA, from which Dr. Thakker obtained the data for his superposition analysis, Actavis listed the data from these same five subjects as "missing." Tr. 591:10-595:25 (Thakker Redirect); PTX 104.764.

After conducting a superposition analysis on the 600 mg Actavis Tablet, Dr. Thakker determined that the C_{min} is [redacted] µg/ml and the C_{max} is [redacted] µg/ml. Tr. 539:9-14 (Thakker Direct). He concluded, therefore, that the MHD steady state blood level for this dose of the Actavis ANDA product falls within the limitations of Claim 6 of the '898 and '131 Patents. Id. at 539:15-22.

Dr. Thakker also concluded that the 600 mg Actavis Tablets are effective in minimizing fluctuations between C_{min} and C_{max} of MHD. Id. at 539:23-540:4. In this context, in Dr. Thakker's expert opinion, minimizing fluctuation requires the ratio of C_{min} to C_{max} to be at least 20%. He developed this understanding by looking at the patent specification, which provides an example of a pharmaceutical formulation that minimizes fluctuations between C_{min} to C_{max} where the steady state MHD levels are between 2 and 10 µg/ml. Id. at 540:5-23; '898 Patent, col. 5, ll. 41-46. According to Dr. Thakker's superposition analysis, the ratio of C_{min} to C_{max} is [redacted] or roughly [redacted]%. Dr. Thakker

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concluded that the 600 mg Actavis Tablet likewise satisfies the limitations of Claim 7 of the '898 and '131 Patents. Tr. 539:23-540:4 (Thakker Direct).

The C_{min} and C_{max} figures that Dr. Thakker reached using superposition analysis also led him to the conclusion that the 600 mg Actavis Tablet satisfies the limitations of Claim 8 of the '898 and '131 Patents. The C_{min} [redacted] µg/ml is within the claim limitation, which requires the C_{min} to be between 2 and 5 µg/ml. The C_{max} [redacted] µg/ml is also within the claim limitation, which requires the C_{max} to be between 6 and 10 µg/ml. Id. at 540:24-541:12.

Although no clinical data regarding the 150 mg and 300 mg Actavis Tablets was available, Dr. Thakker was able to extrapolate the steady state C_{min} and C_{max} values for these tablets using simple arithmetic. Id. at 541:18-542:12. He simply quartered and halved the C_{min} and C_{max} values for the 600 mg to determine the C_{min} and C_{max} values for the 150 mg and 300 mg tablets, respectively. Id. at 542:3-7. Dr. Thakker testified that this was an appropriate method for determining the steady state MHD blood levels for the 150 mg and 300 mg tablets "because the pharmacokinetics for MHD are – you know, are linear with dose, in other words, they are proportional to dose, and this was already indicated by Actavis in their application. So I basically took that information and I just did a simple

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arithmetic operation." Id. at 542:7-12. Moreover, Actavis requested an *in vivo* bioequivalence waiver from the FDA for the 150 mg and 300 mg tablets in light of the data obtained from the 600 mg tablets. PTX 97.3. This, too, supports Dr. Thakker's conclusion. Tr. 544:16-545:5 (Thakker). Actavis's own expert, Dr. Mayersohn agrees that MHD plasma concentration is "a linear system. And a linear system simply means that there is proportionality. If I were to double the dose, I would double the concentration." Tr. 1084:22-25 (Mayersohn Direct).

The Court is not troubled, as Actavis is, by the lack of *in vivo* data for the 150 mg and 300 mg tablets. Dr. Thakker testified persuasively as to the propriety of his calculations and methodology. Furthermore, if Actavis is able to rely upon *in vivo* data for the 600 mg tablets, including data related to MHD blood levels, to support bioequivalence of the 150 mg and 300 mg tablets, Actavis cannot fairly argue that Supernus cannot do the same. Similarly, the Court takes no issue with relying upon the results of a fasted study, as opposed to a fed study. Actavis's draft labeling text for its ANDA tablets explicitly states that extended release oxcarbazepine should be taken on an empty stomach. PTX 98.6.

The C_{min} and C_{max} for the 300 mg tablets are [redacted] µg/ml and [redacted] µg/ml, respectively. Tr. 545:12-15 (Thakker Direct). This falls within the limitations of Claim 6 of the '898 and '131

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Patents. The ratio of C_{min} to C_{max} is also [redacted]%, which fulfills the limitation of "minimizing fluctuations" between C_{min} and C_{max} found in Claim 7 of the '898 and '131 Patents. However, the C_{max} of [redacted] µg/ml does not satisfy Claim 8 of the '898 and '131 Patents. Supernus concedes that it does not assert infringement of Claim 8 of the '898 and '131 Patents by the 300 mg dosage strength of the Actavis Tablets. Plaintiff's Responses to DFOF ("Pl. Resp. DFOF") ¶ 167 [Docket No. 409].

Dr. Thakker determined that the C_{min} and C_{max} for the 150 mg tablets are [redacted] µg/ml and [redacted] µg/ml, respectively. Tr. 545:16-19 (Thakker Direct). These values do not satisfy the limitations of Claims 6 and 8 of the '898 and '131 Patents, although they do meet the limitation of Claim 7 of these patents. In fact, Supernus concedes that it does not assert infringement of Claims 6 and 8 of the '898 and '131 Patents by the 150 mg dosage strength of the Actavis Tablets. Pl. Resp. DFOF ¶ 166.

Dosage	C_{min}	C_{max}	C_{min}/C_{max}
600 mg	[redacted] µg/ml	[redacted] µg/ml	[redacted]%
300 mg	[redacted] µg/ml	[redacted] µg/ml	[redacted]%
150 mg	[redacted] µg/ml	[redacted] µg/ml	[redacted]%

The Court is not persuaded by Actavis's argument that the Court should examine the PK Claims in light of the recommended

daily dose of the Actavis ANDA product. The Actavis ANDA labels and prescribing information state that the "[r]ecommended daily dose is 1,200 mg to 2,400 mg once per day." PTX 388.1; PTX 98.4. The Defendants contend that "if the Actavis product is taken as directed, steady state MHD levels" do not fall within the PK Claims. See Defs. Br. at 18-19. The Court finds no merit in this argument. The Patents-in-Suit make no reference to recommended daily doses, let alone those set forth by Actavis. It would be improper to insert these limitations into the Patents-in-Suit.

Furthermore, as the Plaintiff points out, the Actavis label instructs physicians to "[i]nitiate with a dose of 600 mg once per day" in adults and, in children, to "[i]ncrease in weekly increments of 8 mg/kg to 10 mg/kg once daily, not to exceed 600 mg, to achieve target daily dose." PTX 98.4. In geriatric patients, physicians are instructed to begin "at lower dose (300 mg to 450 mg per day) and increase slowly." Id. Clearly, in some circumstances, the recommended daily dose is 600 mg or lower. "It is well settled that an accused device that 'sometimes, but not always, embodies a claim[] nonetheless infringes.'" Broadcom Corp. v. Emulex Corp., 732 F.3d 1325, 1333 (Fed. Cir. 2013) (quoting Bell Commc'n Research, Inc. v. Vitalink Commc'n Corp., 55 F.3d 615, 622-23 (Fed. Cir. 1995)).

For this reason, too, the Court is not persuaded by Actavis's argument.

Given Dr. Thakker's findings, the Court finds that the Actavis 150 mg tablets do not infringe Claims 6 and 8 of the '898 and '131 Patents and that the Actavis 300 mg tablets do not infringe Claim 8 of the '898 and '131 Patents. The Court, however, holds that all three dosage sizes infringe Claim 7 of the '898 and '131 Patents. The 300 mg and 600 mg tablets infringe Claim 6 of the '898 and '131 Patents. Finally, the 600 mg tablets infringe Claim 8 of the '898 and '131 Patents.

(2) Claim 11 of the '898 and '131 Patents

Claim 11 of the '898 Patent discloses "[t]he formulation of claim 10 in the form of tablets." Claim 10 of the '898 Patent, in turn, reads: "The formulation of claim 1 in the form of pellets, tablets, granules or capsules." Claim 11 of the '131 Patent discloses "[t]he method of claim 10, wherein the formulation is in the form of tablets." Claim 10 of the '131 Patent reads: "The method of claim 1, wherein the formulation is in the form of pellets, tablets, granules or capsules." Claim 10 of each of these patents is dependent upon claim 1.

The Court has already found that the Actavis Tablets infringe Claim 1 of the '898 and '131 Patents. Actavis admits that its ANDA product is a pharmaceutical formulation in the form of tablets. Tr. 597:13-17 (Request for Admission). The

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Actavis Tablets, therefore, infringe both Claim 10, although not asserted, and Claim 11 of the '898 and '131 Patents.

(3) Claims 18 and 19 of the '898 and '131 Patents

Claims 18 and 19 of the '898 and '131 Patents are both dependent on Claim 1 of the respective patents, but include an additional limitation. Claim 18 of both patents requires that, in addition to meeting the limitations of Claim 1, "the polymer having pH-dependent solubility dissolves at pH values of more than 5." The limitation in Claim 19 of both patents requires that "the polymer having pH-dependent solubility dissolves at pH values of more than 6."

The polymers having pH-dependent solubility in the Actavis Tablets are [redacted] and [redacted]. [redacted] dissolves above pH 5.5, thereby satisfying the limitations of Claim 18 of the '898 and '131 Patents. Tr. 663:21-23 (Little Direct); PTX 50.33. [redacted] is soluble at pH levels above 6.0. Tr. 663:24-1; PTX 50.33. This satisfies Claim 19 of both patents. Therefore, Actavis's ANDA product infringes Claims 18 and 19 of the '898 and '131 Patents.

(4) Claim 21 of the '131 Patent

Claim 21 of the '131 Patent reads: "The method of claim 1, wherein the formulation is administered once a day." The parties agree that Actavis's ANDA product is a pharmaceutical

formulation for the treatment of seizures administered once a day. SF p. 11 ¶ 21. Having already found that the Actavis Tablets infringe Claim 1 of the '131 Patent, the Court further holds that the Actavis Tablets also infringe Claim 21 of the '131 Patent.

2. The '600 Patent

The Plaintiffs assert Claims 1, 7 to 9, 12, 18, and 19 of the '600 Patent. The only independent claim in the '600 patent is Claim 1. Each of the remaining asserted claims depends, directly or indirectly, from Claim 1. Claim 1 of the '600 Patent is largely similar to Claim 1 of the '898 Patent. There are, however, critical differences. Claim 1 of the '600 Patent requires a "solid oral pharmaceutical formulation for once-a-day administration of oxcarbazepine comprising a homogeneous matrix," which in turns comprises:

> (a) oxcarbazepine;
>
> (b) 1-50%, by weight of the formulation, a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;
>
> (c) 1-80%, by weight of the formulation, at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and
>
> (d) 10-90%, by weight of the formulation, at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group

> consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, and Eudragit L 100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers,
>
> wherein, in vitro:
>
> (i) between 20 and 74% of the total oxcarbazepine is released by 2 hours; and
> (ii) between 44 and 96% of the total oxcarbazepine is released by 4 hours.

Actavis's ANDA product is admittedly a "solid oral" tablet for once-a-day administration of oxcarbazepine. SF pp. 11-12 ¶¶ 21, 31-32. The Court has held that the Actavis Tablets additionally comprise a homogeneous matrix comprising oxcarbazepine, a matrix-forming polymer as provided in element 1(b), an agent that enhances the solubility of oxcarbazepine as provided in element 1(c), and at least one release promoting agent as provided in element 1(d).

The question the Court now faces is whether the percent weight limitations found in the '600 Patent are infringed. In resolving this question, the Court relies largely on the figures reported by Actavis to the FDA in its Quality Overall Summary regarding the composition of its 150 mg, 300 mg, and 600 mg tablets, reproduced again below. Actavis does not dispute that

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its ANDA product meets element 1(b) of the '600 Patent. SF p. 13 ¶ 38.

Composition of Oxcarbazepine Extended-release Tablets, 150 mg, 300 mg and 600 mg

PTX 116.6

a) Agent that Enhances the Solubility of Oxcarbazepine

This Court has already found that [redacted], present in the Actavis Tablets, acts as an agent that enhances the solubility of oxcarbazepine as required in element 1(c). More importantly, for purposes of this analysis, this Court has held that there is insufficient evidence in the record to support Supernus's position that [redacted] enhances the solubility of oxcarbazepine specifically. [redacted] is found at less than [redacted]% by weight of the formulation in each of the Actavis Tablets. PTX 116.6. [redacted] alone does not satisfy

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element 1(c) of the '600 Patent, which requires 1-80%, by weight of the formulation, of an agent that enhances the solubility of oxcarbazepine. Tr. 694:2-12 (Little Cross). Therefore, having found that the only element 1(c) solubilizing agent in the Actavis Tablets is [redacted], the Court holds that the Actavis Tablets do not infringe element 1(c) of the '600 Patent.

b) Release Promoting Agent

The parties agree that [redacted] and [redacted] are both release promoting agents as required by element 1(d) of each of the Patents-in-Suit. [redacted] and [redacted] are also both polymers having pH-dependent solubility. Together the [redacted] make up [redacted]% by weight of the formulation of the Actavis 150 mg tablet, [redacted]% of the 300 mg tablet, and [redacted]% of the 600 mg tablet. PTX 116.6; Tr. 660:6-18 (Little Direct). These two excipients alone do not satisfy element 1(d) of the '600 Patent, which requires the release promoting agent to be present in an amount from 10% to 90% by weight of the formulation. Tr. 679:2-10 (Little Cross).

Supernus argues, however, that [redacted], found in the Actavis Tablets in the form of [redacted], also acts as an element 1(d) release promoting agent in the Actavis Tablets, despite the fact that it is not a polymer and does not have pH-dependent solubility. See, e.g., Tr. 660:19-661:11 (Little Direct); Tr. 679:11-17

(Little Cross); Tr. 1380:20-24 (Hopfenberg Direct). In support of this position, Supernus directs the Court to the specifications of the Patents-in-Suit which state that "[t]he release promoters are not limited to pH dependent polymers. Other hydrophilic molecules that dissolve rapidly and leach out of the dosage form quickly leaving a porous structure can also be used for the same purpose." '600 Patent, col. 5, ll. 2-6. Therefore, in Supernus's view, the proper reading of element 1(d) does not require all release promoting agents to be polymers with pH-dependent solubility.

Dr. Little testified that [redacted] is "a hydrophilic molecule that people use to put into a formulation and it will dissolve away leaving a pore," in the manner described in the specification. Tr. 660:25-661:11 (Little Direct). By weight of the formulation, it makes up [redacted]%, [redacted]%, and [redacted]% of the Actavis 150 mg, 300 mg, and 600 mg tablets, respectively. PTX 116.6. [redacted], combined with the [redacted], is present in an amount over 10% by weight of the formulation in each of the Actavis Tablets. The Court must evaluate, however, the propriety of including [redacted] in this analysis.

The parties dispute the scope of the claim language, particularly the word "comprising." Claim element 1(d) of the '600 Patent requires "10-90%, by weight of the formulation, at

least one release promoting agent comprising a polymer having pH-dependent solubility selected from" a group of polymers. On the one hand, Actavis argues that only polymers with pH-dependent solubility may satisfy this element. Defs. Br. at 17-18. Supernus, on the other hand, contends that molecules that act as release promoters, even if they are not polymers with pH-dependent solubility, may meet this limitation because the word "comprising" is "an open-ended term of art in patent law that does not exclude additional, unrecited elements." Plaintiff's Post-Trial Brief ("Pl. Br.") at 25 [Docket No. 394].

Dr. Little testified that when he reads element 1(d) of each of the Patents-in-Suit, he first "[breaks] it down into several pieces[.]" Tr. 658:14-17 (Little Direct). Under his reading, "[t]he requirement [in element 1(d) of the '600 Patent] would be the formulation must contain 10 to 90 percent by weight of one or more release promoting agents of any type." Id. at 658:22-24. He then continued: "Following at least one release promoting agent is comprising a polymer having pH-dependent solubility. So, my read on that is that at least one release promoting agent must include at least one polymer having pH-dependent solubility but may include other release promoters." Id. at 658:25-659:4. This is a construction that Dr. Little formulated along with counsel for Supernus. Tr. 676:19-678:5 (Little Cross).

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While the Court is skeptical of Supernus's reading of the claim language, and is hampered by having no claim construction hearing on this term, it need not resolve this issue because, regardless of the scope of the claim language, Supernus has not carried its burden of proving by a preponderance of the evidence that [redacted] acts a release promoting agent in the Actavis Tablets. Assuming that the Plaintiff is correct that element 1(d) encompasses "[o]ther hydrophilic molecules that dissolve rapidly and leach out of the dosage form quickly leaving a porous structure," '898 Patent, col. 4, ll. 64-67, the Court holds that Supernus has not established by a preponderance of the evidence that [redacted] is such a molecule.

Supernus relies almost exclusively upon the testimony of Dr. Little to establish that [redacted] acts as an element 1(d) release promoting agent. Dr. Little testified that "[redacted] is a hydrophilic molecule that people use to put into a formulation and it will dissolve away leaving a pore. . . . it's actually a very similar mechanism that's discussed in the specification for how the release promoter functions, by dissolving and leaving pores that would then work together with the other pieces of the (a) through (d) in order to produce an enhanced formulation." Tr. 661:2-11 (Little Direct). He did not elaborate on his experience or familiarity with [redacted] or its release promoting properties.

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Additionally, he did not explain who the "people" who use [redacted] in their formulations are. Aside from this testimony, there is a dearth of other evidence in the record supporting the Plaintiff's position that [redacted] acts as a release promoter, as contemplated by the patent specifications, in the Actavis Tablets.

On cross-examination, Dr. Little confirmed that, assuming all the other limitations were met, "a formulation [with] a trivial amount of pH-dependent polymer and ten percent [redacted] would infringe the '600 Patent. See Tr. 680:16-681:17 (Little Cross). Yet, in spite of its potentially central role, the evidence regarding [redacted] is sparse. Notably, the record is devoid of any references of testing or experimentation conducted by Dr. Little or any others involved in this litigation regarding the release promoting characteristics of [redacted] generally or in the Actavis Tablets.

Dr. Hopfenberg likewise testified that his "experience is limited to the fact that [redacted] is not a polymer and it dissolves rapidly." Tr. 1456:5-8 (Hopfenberg Cross). He continued: "I never witnessed a formulation where it [redacted] leaches out [of] the dosage form quickly leaving a porous structure that can be used for the same purpose. I have no experience with that specific experiment." Id. at 1456:8-12.

His lack of familiarity with [redacted] properties only serves to highlight the Court's concerns.

The Court finds that the limited evidence put forth by the Plaintiff regarding [redacted] is insufficient to carry its burden of proof as to element 1(d) of the '600 Patent.

Therefore, for the reasons set forth above, the Court holds that that the Actavis Tablets do not infringe Claim 1 of the '600 Patent, as Supernus has failed to meet its burden of proving infringement as to claim element 1(c) and 1(d). Having found no infringement of independent Claim 1 of the '600 Patent, the Court need not address the remaining dependent claims. Ferring B.V. v. Watson Labs., Inc.-Florida, 764 F.3d 1401, 1411 (Fed. Cir. 2014); Monsanto, 503 F.3d at 1359 ("One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that claim."). There is, therefore, no infringement of the '600 Patent by any of the Actavis Tablets.

C. Invalidity

A patent and each of its claims are presumed to be valid, even where those claims may be dependent upon other invalid claims in the patent. 35 U.S.C. § 282(a). A party may rebut this presumption of validity with clear and convincing evidence of invalidity. Sciele Pharma Inc. v. Lupin Ltd., 684 F.3d 1253, 1260 (Fed. Cir. 2012) (citing 35 U.S.C. § 282 and Microsoft

Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238, 2245 (2011)). To be clear, the burden of establishing invalidity by clear and convincing evidence remains on the party asserting invalidity. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1078 (Fed. Cir. 2012). "The 'clear and convincing' standard of proof of facts is an intermediate standard which lies somewhere between 'beyond a reasonable doubt' and a 'preponderance of the evidence' . . . [and] has been described as evidence which produces in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contentions are highly probable.'" Buildex Inc. v. Kason Indus., Inc., 849 F.2d 1461, 1463 (Fed. Cir. 1988) (quoting Colorado v. New Mexico, 467 U.S. 310, 316 (1984)).

Where an invalidity challenge is based upon prior art that was considered by the PTO during the patent prosecution, and where a patent was issued notwithstanding the prior art, "a court owes some deference to the PTO's decision." Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1572 (Fed. Cir. 1992) (citations omitted). Although a defendant's burden does not change, evidence considered by the PTO may not be given the same weight as new evidence. See Sciele Pharma, 684 F.3d at 1260 ("[N]ew evidence not considered by the PTO 'may carry more weight . . . than evidence previously considered by the PTO,' and may 'go further toward sustaining

the attacker's unchanging burden.'") (quoting Microsoft Corp., 131 S. Ct. at 2251).

As a defense to infringement, the Defendants assert the following grounds for invalidity: obviousness, lack of written description, and indefiniteness.

1. Obviousness

A patent is invalid as obvious if the differences between the claimed invention and the prior art are such that the invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made. Sciele Pharma, 684 F.3d at 1259 (quoting 35 U.S.C. § 103(a)). Whether a patent claim is obvious is a question of law based on four underlying facts: (1) the scope and content of the prior art; (2) the differences between the prior art and the claim at issue; (3) the level of ordinary skill in the pertinent art; and (4) such secondary considerations as commercial success, long-felt but unmet need, and the failure of others. Id. (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)); see also KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 406 (2007).

Generally, this inquiry considers whether a person skilled in the art would have had (1) reason to combine the teachings of the prior art references to achieve the claim invention, and (2) a reasonable expectation of success in doing so. In re Cyclobenzaprine, 676 F.3d at 1068-69 (internal citations

omitted). "[O]bviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." In re O'Farrell, 853 F.2d 894, 903-04 (Fed. Cir. 1988); see also Bayer Schering Pharma AG v. Barr Labs., Inc., 575 F.3d 1341, 1350 (Fed. Cir. 2009); Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007).

In KSR, the Supreme Court cautioned that this inquiry must be "expansive and flexible" and must account for the fact that a person of ordinary skill in the art is also "a person of ordinary creativity, not an automaton." 550 U.S. at 415, 421. There need not be "precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." Id. at 418.

Importantly, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." Id. at 417. Relevant to this analysis is whether there was a reason or motivation to combine the known elements in the manner claimed by the patent. Id. at 418. Indeed, "[o]ne of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at

the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." Id. at 419-20. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. at 420.

Finally, an invention is "obvious-to-try" and therefore invalid under 35 U.S.C. § 103 if it results from a skilled artisan merely pursuing "known options" from "a finite number of identified, predictable solutions." In re Cyclobenzaprine, 676 F.3d at 1070 (quoting KSR, 550 U.S. at 421) (internal quotations omitted). It is crucial to keep in mind, however, that "knowledge of [a] a goal does not render its achievement obvious." Abbott Labs. V. Sandoz, Inc., 544 F.3d 1341, 1352 (Fed. Cir. 2008).

The Defendants contend that the asserted claims are obvious in light of a combination of prior art references setting forth oxcarbazepine and extended-release carbamazepine formulations for the treatment of seizures. The Court will address each of the prior art references in turn.

The Court will first address the scope and content of the prior art, as well as the differences between the claimed invention and the prior art. Next, the Court will assess whether a skilled artisan would have been motivated to combine the teachings of the prior art to formulate oxcarbazepine once

daily, and whether such a person would have had a reasonable expectation of success in doing so. Finally, the Court will evaluate the objective indicia of non-obviousness, or secondary considerations, and then set forth its conclusions of law.

a) Scope and Content of the Prior Art and Differences between the Prior Art and the Claimed Invention

By 2006, as described above, several drugs for the treatment of seizures were available on the market, including immediate release oxcarbazepine formulations and both immediate and extended release carbamazepine formulations. While immediate release oxcarbazepine has been available since 2000 and other AEDs have been reformulated as extended release, once daily products, no effective once daily oxcarbazepine formulation was developed prior to 2006.

At the time of Supernus's invention, it was well known that significant and material differences exist between carbamazepine and oxcarbazepine. See, e.g., PTX 327.18; PTX 341; Tr. 1700:11-1710:25 (Thakker Direct). The peer-reviewed literature and prior art also established that obstacles exist to creating an effective once daily oxcarbazepine formulation. See, e.g., PTX 230.3; DTX 199 at ACT-OXXR002756316.

Notwithstanding these impediments, the Defendants argue that, in light of a combination of prior art references, Supernus's once daily formulation of oxcarbazepine to treat

seizures was obvious. The Defendants rely upon several prior art references disclosing AED formulations, including one oxcarbazepine formulation and several carbamazepine formulations, as well as a prior art reference disclosing extended release antimicrobial agents.

(1) The Franke Patent

The only oxcarbazepine formulation the Defendants identify in the prior art is International Publication No. WO 03/101430 (the "Franke Patent"). DTX 199. Actavis argues, through Dr. Mayersohn, that the Franke Patent "show[ed] that one can create a once-a-day form of oxcarbazepine." Tr. 1132:2-3 (Mayersohn Cross); see also Tr. 1090:18-1092:7 (Mayersohn Direct).

The Patent Examiner, however, considered the Franke Patent during the prosecution of the Patents-in-Suit and found that Supernus's invention was not covered by the prior art. See PTX 5.219-20; PTX 1.2; PTX 2.2; PTX 3.2; Tr. 1138:7-8 (Mayersohn Cross). Actavis, therefore, has "the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents." Shire LLC v. Amneal Pharm., LLC, 802 F.3d

1301, 1307 (Fed. Cir. 2015). The Court finds that Actavis has not met this burden.

According to Dr. Mayersohn, the blood level concentration profile disclosed in the Franke Patent after a single dose would "allow a person of ordinary skill to reach a reasonable conclusion that that would provide once-a-day therapy if multiple dosed." Tr. 1139:13-16, 1145:9-15 (Mayersohn Cross). Apydan® Extent, the only commercial embodiment of the Franke Patent, however, is a twice daily formulation. Id. 1133:20-1134:2. In fact, the specifications of the Patents-in-Suit distinguish the present invention from the Franke Patent, observing that "the solubility and bioavailability of the drug from [the Franke Patent] [was not] suitable for once-a-day administration." '898 Patent, col. 2, ll. 12-14.

Dr. Mayersohn went so far as to testify that "from a lot of the patents that [he has] reviewed," he believes that nearly any invention for once daily administration is obvious if it has previously been formulated for twice daily administration. Tr. 1148:2-8, 1151:6-14 (Mayersohn Cross). As Supernus correctly points out, "[a]lmost any invention, no matter how nonobvious at the time, will appear obvious when looking backward from the solution." Pl. Br. at 30 (citing Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc., 456 F. Supp. 2d 644, 662 (D.N.J. 2006)). The Court does not credit this "hindsight reconstruction" in its

obviousness analysis. See Janssen, 456 F. Supp. 2d at 662. Likewise, the fact that a goal is known "does not render its achievement obvious." Abbott Labs., 544 F.3d at 1352.

The Court is instead persuaded by Supernus that the Franke Patent discloses immediate-release twice-a-day oxcarbazepine formulations and teaches away from once daily administration of oxcarbazepine. The Franke Patent teaches ***in vitro*** release profiles wherein 90-100% of the oxcarbazepine is released in sixty minutes, indicating an immediate release profile. DTX 199 at ACT-OXXR002756316-17; Tr. 1653:7-18 (Little Direct). Dr. Little testified that the Franke Patent "is an immediate-release product." Id. at 1653:14. In fact, the Franke Patent itself states: "The result is surprising because the in vitro release curve of oxcarbazepine of the compositions according to this invention is only slightly below that of the commercial [immediate-release, twice daily] tablets in which no adequate prolongation of the effect is normally expected." DTX 199 at ACT-OXXR002756316. Dr. Hopfenberg agreed that the ***in vitro*** release profile in the Franke Patent "would not have been viewed by a person of ordinary skill in the art as likely to provide 24 hours of therapy." Tr. 1497:10-1499:1 (Hopfenberg Cross). What's more, the Franke Patent explicitly observes that oxcarbazepine formulations with controlled release profiles, such as those that release approximately 40% of the

oxcarbazepine within 60 minutes "turned out to be ineffective." DTX 199 at ACT-OXXR002756316.

Furthermore, the Franke Patent does not teach the use of element 1(c) agents that enhance the solubility of oxcarbazepine. Tr. 1654:14-20 (Little Direct).

(2) The Carbamazepine Prior Art

The Katzhendler and two Rudnic Patents (as defined below) relied upon by the Defendants are directed to carbamazepine formulations. Dr. Hopfenberg testified that if a person skilled in the art were attempting to develop an extended release oxcarbazepine formulation, the person would look to prior art involving other materials that are similar to oxcarbazepine in terms of use, solubility, and molecular structure, such as carbamazepine. Tr. 1409:617 (Hopfenberg Direct). Dr. Hopfenberg premised his obviousness opinions on the similarities between oxcarbazepine and carbamazepine, essentially treating them as interchangeable. See Tr. 1445:4-13 (Hopfenberg Cross). Dr. Hopfenberg testified that his understanding is that "Carbamazepine, oxcarbazepine are identical except for the carbonyl group." Id. at 1451:6-8.

The presence of a carbonyl group in oxcarbazepine, however, is a critical difference that impacts how the molecule interacts with water. See id. at 1448:3-5. In addition to this, the literature establishes many other significant differences

between oxcarbazepine and carbamazepine that undermine the Defendants' obviousness argument. The 2003 article by Theodor May et al. entitled Clinical Pharmacokinetics of Oxcarbazepine, explained that although oxcarbazepine and carbamazepine have similar chemical structures, "significant differences exist in pharmacokinetics and drug interactions between these two drugs." PTX 327.18. The authors caution that oxcarbazepine and carbamazepine "should be considered as distinct therapeutic agents." Id. Another article published in 2004 by Dieter Schmidt and Christian E. Elger, entitled What is the evidence that oxcarbazepine and carbamazepine are distinctly different antiepileptic drugs?, described the differences between oxcarbazepine and carbamazepine as including differences in "mode of action and metabolism, but also, in particular, in terms of the proven efficacy and good tolerability of [oxcarbazepine]." PTX 341.7.

Moreover, Dr. Thakker testified as to the differences between how the body absorbs, distributes, metabolizes, and excretes oxcarbazepine and carbamazepine. See Tr. 1700:11-1710:25 (Thakker Direct) ("[T]he two compounds . . . certainly [once] th[ey] get into the body are processed by the body with respect to all four processes, absorption, it's distribution, it's metabolism and it's elimination . . . the body really treats them as very, very different compounds."). Dr. Thakker

identified, for example, the vastly different half-lives of the two compounds. While carbamazepine has a half-life between twenty-five and eighty-five hours, oxcarbazepine's half-life is roughly two hours. Id. at 1709:20-1710:12, 1710:20-25.

Dr. Hopfenberg, on the other hand, did not consider the chemical, pharmacokinetic, and other differences between carbamazepine and oxcarbazepine. See Tr. 1445:19-1447:19, 1448:18-22, 1451:9-11 (Hopfenberg Cross). Given that Dr. Hopfenberg's obviousness analysis is premised on the false assumption that oxcarbazepine is interchangeable with carbamazepine, the Court finds that Actavis has not met its burden of demonstrating the prior art directed to carbamazepine renders the Patents-in-Suit obvious. Nonetheless, the Court will address in more detail the Katzhendler and Rudnic Patents.

The Katzhendler Patent

U.S. Patent No. 6,296,873 (the "Katzhendler Patent") teaches sustained release formulations of carbamazepine and certain carbamazepine derivatives. DTX 114. As with the Franke Patent, the PTO considered the Katzhendler Patent during prosecution of the Patents-in-Suit and issued the Supernus Patents notwithstanding.

Actavis posits that since the Katzhendler Patent specification lists oxcarbazepine first on a list of carbamazepine derivatives, the teachings of this patent are

directed to extended release oxcarbazepine formulations. Tr. 1404:4-13 (Hopfenberg Direct). Supernus correctly emphasizes, though, that aside from this list, the Katzhendler Patent "does not otherwise mention oxcarbazepine or provide any direction to select oxcarbazepine for a once-a-day product." Pl. Br. at 35.

As outlined above, however, there are noteworthy and numerous differences between carbamazepine and oxcarbazepine. The Katzhendler Patent itself also indicates that the two compounds are not interchangeable. The Katzhendler Patent specification explains that the "preferred" release accelerating agent is polyethylene glycol. DTX 114 at col. 10, ll. 28-30. Oxcarbazepine, though, is not compatible with polyethylene glycol, demonstrating that oxcarbazepine and carbamazepine are not simply interchangeable. See, e.g., PTX 356.24; Tr. 1660:21-1661:3, 1663:6-19 (Little Direct) (testifying that excipient compatibility studies show that polyethylene glycol degrades oxcarbazepine); Tr. 72:11-74:10 (Bhatt Direct).

Moreover, the Katzhendler Patent teaches away from the use of release promoting polymers with pH-dependent solubility, which are required in element 1(d) of the Patents-in-Suit. The Katzhendler Patent, instead, calls for polymers that inhibit release and "slow[] down the water penetration into the tablet and thus slow[] the tablet erosion." DTX 114 at col. 9, ll. 45-62. Additionally, the Katzhendler Patent is directed to

pharmaceutical formulations with zero-order release profiles, meaning linear or straight release profiles. Tr. 1661:8-1663:19 (Little Direct). Polymers with pH-dependent solubility are necessarily inconsistent with zero-order release profiles and, therefore, with the Katzhendler Patent's teachings. Id. Such a modification would be improper. See Plas-Pak Indus., Inc. v. Sulzer Mixpac AG, 600 F. App'x 755, 758 (Fed. Cir. 2015) ("[C]ombinations that change the basic principles under which the prior art was designed to operate, or that render the prior art inoperable for its intended purpose, may fail to support a conclusion of obviousness.") (internal quotations, citations, and modifications omitted).

The Rudnic Patents

Actavis likewise relies on U.S. Patent No. 5,325,570 (the "Rudnic '570 Patent") and U.S. Patent No. 5,912,013 (the "Rudnic '013 Patent and, collectively, the "Rudnic Patents"). DTX 113; DTX 344. The Rudnic Patents are also directed to carbamazepine formulations and contain no teachings regarding oxcarbazepine. Tr. 1495:9-20 (Hopfenberg Cross). The carbamazepine formulations disclosed in the Rudnic Patents are multiple unit, or pellet, dosage forms for administration "preferably twice a day." DTX 113 at col. 1, ll. 44-45, col. 2, ll. 62-64. Carbatrol®, a commercial embodiment of the Rudnic Patents, is

administered twice daily. Tr. 1487:24-1488:14 (Hopfenberg Cross).

In addition to having a different dosing frequency and active ingredient than the Patents-in-Suit, the Rudnic Patents also teach away from a homogeneous matrix tablet. The formulations in the Rudnic Patent require "three different units in order for [them] to work." Tr. 1664:8-25 (Little Direct). Rather than having all the constituents uniformly dispersed across a matrix tablet, the formulations disclosed in the Rudnic Patents include separate pellets in each dose. Multi-pellet formulations are not homogeneous matrix formulations. Id.

Dr. Hopfenberg opined that a person of ordinary skill in the art would rely on the formulation of Pellet C described in the Rudnic '570 Patent, in combination with other prior art references, to arrive at a once daily oxcarbazepine homogeneous matrix tablet. Tr. 1415:9-1420:10 (Hopfenberg Direct); Tr. 1495:25-1496:4 (Hopfenberg Cross). The dissolution profile of Pellet C is also vastly different from that disclosed in the Supernus Patents. DTX 113 at Fig. 1; Tr. 1496:15-21 (Hopfenberg Cross).

The Court agrees with the Plaintiff that the Defendants have "failed to explain how or why a formulator would select one of the dozens of **carbamazepine** pellets disclosed in Rudnic and modify that particular pellet to arrive at Supernus's claimed

oxcarbazepine formulations." Pl. Br. at 37 (emphasis in original). Additionally, Dr. Hopfenberg could recall no examples teaching that Pellet C alone could be efficaciously administered. Tr. 1497:4-9 (Hopfenberg Cross).

The Oren Patent

Finally, the Defendants rely upon European Patent Publication No. 0 280 571 (the "Oren Patent") as prior art. DTX 390. The Oren Patent discloses sustained release matrix formulations of antimicrobial agents. DTX 390 at p. 2. It is unrelated to oxcarbazepine, carbamazepine, or any other anti-epileptic drug. Tr. 1499:12-13 (Hopfenberg Cross). The Oren Patent does not disclose a homogeneous matrix. Id. at 1491:9-14. The Court agrees with Dr. Little that there is no reason for a person of ordinary skill in the art to consult the Oren Patent in attempting to formulate a once daily oxcarbazepine formulation comprising a homogeneous matrix. See Tr. 1665:11-14 (Little Direct).

b) Motivation to Combine Prior Art References to Formulate Once-Daily Oxcarbazepine Treatment for Seizures & Reasonable Expectation of Success

The Defendants put forth evidence to demonstrate that a person skilled in the art would have been motivated to develop an extended-release oxcarbazepine drug for the treatment of seizures. For example, Dr. Mayersohn testified regarding the

commercial motivation to develop an extended-release oxcarbazepine drug based on the development of extended-release formulations of other drugs used to treat seizures. Tr. 1077:1-20 (Mayersohn Direct). Carbamazepine and divalproex entered the market as immediate-release anti-epileptic drugs in the 1960s. Extended-release formulations of carbamazepine entered the market under the brand names Tegretol XR® and Carbatrol® in the 1990s. An extended-release formulation of divalproex has been available since 2000, marketed under the name Depakote ER®. Id. at 1077:7-14. Immediate-release oxcarbazepine in the form of Trileptal® has been available and known to treat seizures since 2000. Dr. Mayersohn testified that, based on the progression of other anti-epileptic drugs, a person of ordinary skill in the art would have clearly been motivated to make an extended-release formulation of oxcarbazepine and that the prior art predicted the ability to do so. Id. at 1077:15-20.

Actavis's position, however, disregards the prior art and literature suggesting that oxcarbazepine is not suitable for an extended release formulation. The mere fact that a goal is known and desired does not lead to the conclusion that its achievement is obvious. Abbott Labs., 544 F.3d at 1352. And yet, in coming to his obviousness opinion, Dr. Mayersohn did not examine any scientific impediments to making a once daily

oxcarbazepine formulation because it was "not important" to his analysis. Tr. 1126:10-19 (Mayersohn Cross).

On the contrary, such impediments are critical to the question of whether a person of ordinary skill in the art would be motivated to combine certain prior art references. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, 550 U.S. at 418. "[T]he law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention." Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1361 (Fed. Cir. 2011).

In this Court's opinion, Supernus's concession that "[t]he need for a controlled-release dosage form for drugs taken chronically such as oxcarbazepine and derivatives is self-evident," '898 Patent, col. 1, ll. 33-35, is more probative of long-felt need than obviousness or the motivation of a person skilled in the art to combine the prior art references to develop a once daily extended release oxcarbazepine formulation. While Dr. James Wheless testified that "[t]he next obvious kind of thought" was to make an extended release oxcarbazepine formulation, Tr. 1190:18-20 (Wheless Direct), this says little about motivation of a person of ordinary skill in the art to

combine the teachings of the prior art that the Defendants have identified to create this desired formulation.

Contrary to Actavis's position, Supernus did "show that oxcarbazepine had [certain] peculiar characteristics known in the prior art that would 'demotivate' the POSA from starting down the path toward developing a once-daily formulation." Defs. Br. at 22. For example, the 2000 Collins and Garnett article, entitled Extended Release Formulations of Anticonvulsant Medications: Clinical Pharmacokinetics and Therapeutic Advantages, explained that "oxcarbazepine would not be an appropriate candidate [for extended release development] because it is essentially a prodrug and is rapidly and extensively metabolized to its primary active metabolite.[23] It is recommended that oxcarbazepine is administered twice daily." PTX 230.3; Tr. 1694:11-15 (Thakker Direct). Dr. Thakker testified that, given the fact that oxcarbazepine is "essentially a prodrug," a person skilled in the art would not be motivated to formulate a once daily oxcarbazepine

[23] When asked to describe a prodrug, Dr. Thakker explained: "So, we know that oxcarbazepine, even during its absorption, it extensively gets metabolized in the liver and it produces the hydroxyl, monohydroxy which we call MHD, and the majority of the pharmacological activity of oxcarbazepine is really attributed to the MHD. So, whenever you have a drug that you administer and it produces another chemical entity as a result of metabolism, which is then the pharmacological entity, we generally refer to that as a prodrug." Tr. 1693:1-11 (Thakker Direct).

formulation, despite the theoretical desirability of such a product. Tr. 1694:23-1695:2 (Thakker Direct). In fact, Oxtellar XR® "is the only epilepsy medication we have that's ever been a prodrug that's been able to be made into an extended-release product." Tr. 1216:8-13 (Wheless Direct).

Additionally, oxcarbazepine exhibited an "absorption window," which resulted in bioavailability obstacles for formulators attempting to create an extended-release once daily oxcarbazepine AED. Tr. 1697:18-23 (Thakker Direct). Due to the absorption window, oxcarbazepine's bioavailability and effectiveness decreases when it is released outside of this absorption window. See PTX 224.1; Tr. 56:4-20, 57:23-60:13 (Bhatt Direct). Oxcarbazepine's absorption window was observed not only by the Jazz formulators, see, e.g., PTX 224.1; Tr. 56:14-20 (Bhatt Direct), but it was also encountered in the Franke Patent. See Tr. 1697:18-1700:1 (Thakker Direct). The Franke Patent states that "Typical controlled-release formulas with a low subsequent ***in-vitro*** release profile (60 min: about 40% oxcarbazepine release) however turned out to be ineffective." DTX 199 at ACT-OXXR00275316. Dr. Thakker credibly testified that the controlled-release formulas that the Franke Patent inventors found to be ineffective suffered from "performance [that] was poor in terms of absorption of the

active ingredient" as a result of oxcarbazepine's absorption window. Tr. 1699:19-1700:1 (Thakker Direct).

Moreover, Dr. Thakker testified that significant experimentation would be required to identify the specific absorption window of oxcarbazepine, as the specific contours of the obstacle were not identified or overcome in the prior art. See Tr. 1716:16-1718:10 (Thakker Cross). "Without the knowledge of a problem, one of skill in the art would not have been motivated to modify" the prior art to solve the problem. Novartis Pharm. Corp. v. Watson Labs., Inc., 611 F. App'x 988, 996 (Fed. Cir. 2015).

Defendants rely upon Allergan, Inc. v. Watson Labs., Inc. – Florida, 869 F. Supp. 2d 456, 483 (D. Del.) aff'd, 470 F. App'x 903 (Fed. Cir. 2012) to demonstrate that an absorption window impediment is no impediment at all. However, in Allergan, the district court explained that "persons of skill in the art had numerous references available that addressed trospium's positive attributes as well as how to remedy trospium's negative attributes." Id. Here, no prior art has been identified that details "how to remedy [oxcarbazepine's] negative attributes."

Finally, Supernus is correct that the evidence "includes reports of unequivocal failures by skilled formulators trying to develop a once-a-day oxcarbazepine product." Pl. Br. at 30. For instance, Dr. Bhatt testified that the Jazz Pharmaceuticals

and Shire joint venture was terminated when the formulators were unsuccessful in developing an effective once-a-day oxcarbazepine formulation. See, e.g., Tr. 57:23-60:13 (Bhatt Direct). Likewise, Actavis developed over one hundred different experimental formulations in its attempt to develop a generic once daily oxcarbazepine drug before it developed the accused product. See, e.g., Tr. 1642:1-7, 1643:14-1651:8 (Little Direct); PTX 72.12-14, 26-28. "While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure." In re Cyclobenzaprine, 676 F.3d at 1081 (quoting Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir. 2003)).

c) Secondary Considerations

As the Court concludes that Actavis has failed to meet its burden of proving obviousness, the Court need not address the objective indicia of non-obviousness, or secondary considerations. Nonetheless, it will do so.

"[S]econdary considerations [such] as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented" and "may have relevancy" as indicia as obviousness or non-obviousness. Graham, 383 U.S. at 17-18. "A nonmovant may rebut a prima facie

showing of obviousness with objective indicia of nonobviousness." Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006) (citing WMS Gaming, Inc. v. Int'l Game Tech., 184 F.3d 1339, 1359 (Fed. Cir. 1999); In re Kahn, 441 F.3d 977, 990 (Fed. Cir. 2005)).

(1) Long Felt But Unmet Need

Dr. Wheless testified as to the secondary considerations supporting non-obviousness. Dr. Wheless is the former Chief of Pediatric Neurology at St. Jude's Children's Hospital and current Chief of Pediatric Neurology at the University of Tennessee Health Science Center and Director of Le Bonheur Neuroscience Institute and Comprehensive Epilepsy Program. PTX 524. He has treated over one hundred patients with Oxtellar XR® since its commercial release. Tr. 1183:17-21 (Wheless Direct). He has also converted patients from Trileptal®, the twice daily oxcarbazepine formulation, to Oxtellar XR® and has observed better tolerance for increased dosages in many of those patients. Id. at 1187:10-20. Some of his patients who continued to have seizures while taking Trileptal® finally achieved seizure freedom after taking Oxtellar XR®. Id. at 1187:17-20. Dr. Wheless has never switched a patient from Oxtellar XR® to Trileptal®. Id. at 1187:21-23.

In Dr. Wheless's opinion, as an expert in neurology and the treatment of epilepsy, Oxtellar XR® satisfied a long felt but

previously unmet need for an extended release, once daily oxcarbazepine formulation for the treatment of seizures. See, e.g., id. at 1189:2-5. Oxcarbazepine was first released in an immediate-release formulation in 2000. While this in itself was an improvement over other anti-epileptic drugs, such as carbamazepine, Dr. Wheless explained, there was still a need to reduce side effects, improve tolerability, and increase patient adherence and compliance. Id. at 1190:18-24.

According to Dr. Wheless, Oxtellar XR® satisfied these needs. Patients taking Oxtellar XR® report fewer side effects than those taking carbamazepine or twice daily oxcarbazepine. Id. 1191:5-12. Dr. Wheless's patients also displayed improved tolerability on Oxtellar XR® as opposed to immediate release oxcarbazepine. Id. at 1192:5-14. The results of Supernus's Phase III clinical trials for Oxtellar XR® also support this conclusion. PTX 388.8-12. The results indicated that the incidence for any given side effect was roughly fifty percent lower for patients on Oxtellar XR® as compared to those on immediate release oxcarbazepine. Tr. 1193:18-24 (Wheless Direct); PTX 388.9-11. Dr. Wheless testified that it is rare, if not unheard of, for the FDA to include such comparisons in product labels. Tr. 1194:13-19 (Wheless Direct). While the FDA's inclusion of this comparison in the Oxtellar XR® label is "unique," id., this information is useful because, "as a

practitioner, it's helpful to see the side-by-side side effect profile when I think about prescribing this product to realize there are two distinctly different products, that one has a better side effect profile." Id. at 1195:20-25.[24]

Patients taking Oxtellar XR® also demonstrated improved adherence. Dr. Wheless attributed this in part to the reduced incidence of side effects, which causes fewer disruptions in patients' lives. With fewer side effects, patients are more likely to be diligent about taking their medication even before important meetings or school, for example. Id. at 1199:11-21. Given the high stakes involved, improving patient compliance is of critical importance. Id. at 1201:7-19.

The Court, however, appreciates the Defendants' point that "[t]here is still, today, an ongoing need for more and better AEDs." DFOF ¶ 401 (citing Tr. 1249:17-24 (Lado Direct)). Certainly, Oxtellar XR® may not have resolved every long felt need related to the treatment of epilepsy and the Court does not doubt Actavis's view that there continues to be room for further

[24] The Court notes, as did Actavis, that the Oxtellar XR® label also cautions against directly comparing adverse event frequencies because the immediate release oxcarbazepine and Oxtellar XR® were not examined in the same trial. PTX 388.10. While these comparisons should perhaps be viewed with some skepticism, the Court, however, agrees with Dr. Wheless that the comparison is a relevant one, both for prescribing physicians and for the analysis of secondary considerations. See Tr. 1221:16-1222:8 (Wheless Cross).

improvement and development of AEDs. That being said, Supernus has identified a long felt need for an extended release, once daily formulation of oxcarbazepine to treat seizures that results in an improved side effect profile, as well as increased tolerability and patient compliance. The Court further finds that Oxtellar XR® met this need.

(2) Industry Skepticism

"General skepticism of those in the art – not amounting to teaching away – is also 'relevant and persuasive evidence' of nonobviousness." Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 885 (Fed. Cir. 1998) (quoting Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 726 (Fed. Cir. 1990)). The Court finds that Supernus has established industry skepticism that an effective once daily oxcarbazepine formulation for the treatment of seizures could be developed.

Dr. Wheless testified that, in light of Dr. Bhatt's testimony and peer-reviewed literature regarding twice daily Apydan® Extent, there was industry skepticism that an effective once daily oxcarbazepine formulation could be developed. Tr. 1212:10-14 (Wheless Direct). While the "reformulation of immediate-release anti-epileptic drugs into extended release formulations has been part of the life-cycle of such drugs," Defs. Br. at 29, there is no certainty that such a goal can be achieved since each active ingredient exhibits different

properties that may impede the development of an extended release version.

The 2007 Meir Bialer article, for example, demonstrated the industry's view that oxcarbazepine did not "fit the model for once daily administration." Id. at 1213:14-18; PTX 555. The Franke Patent similarly counseled that controlled-release oxcarbazepine formulations "turned out to be ineffective." DTX 199 at ACT-OXXR002756316. The 2000 Collins and Garnett article also stated that "Oxcarbazepine would not be an appropriate candidate [for extended release formulation] because it is essentially a prodrug and is rapidly and extensively metabolized to its primary active metabolite. It is recommended that oxcarbazepine is administered twice daily." PTX 230.3. Finally, after its formulators were unable to develop an effective once daily oxcarbazepine formulation, Jazz terminated its joint venture with Shire, demonstrating, in both Dr. Bhatt and the Court's opinions, its skepticism that such an objective could be achieved. See Tr. 64:9-19, 65:25-66:6 (Bhatt Direct).

(3) Failure of Others

Evidence of the failure of others may be "determinative on the issue of obviousness." Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1285 (Fed. Cir. 2000). There is no dispute that Supernus developed and marketed the first once

daily extended release oxcarbazepine formulation for the treatment of seizures.

Dr. Wheless concluded that, before Supernus succeeded, others had attempted to formulate a once daily oxcarbazepine to treat seizures, but failed. Tr. 1202:19-21 (Wheless Direct). He based his opinion upon his own experience as a neurologist and epileptologist, peer-reviewed literature, and Apydan® Extent, the commercial embodiment of the Franke Patent. Id. at 1202:21-25. For example, Dr. Wheless testified that he had discussions with representatives of Novartis, the pharmaceutical company that developed the immediate release oxcarbazepine formulation known as Trileptal®, regarding extended release formulations. Id. 1204:25-1205:6. To date, Novartis has not marketed an extended release oxcarbazepine formulation. While this may be an interesting observation, this Court does not find that this alone supports the position that Novartis tried and failed to formulate an extended release oxcarbazepine product.

There is, however, evidence that the Franke Patent inventors attempted, but failed to formulate an effective once daily oxcarbazepine product. See, e.g., id. at 1206:19-22; Tr. 1697:25-1700:1 (Thakker Direct). Dr. Wheless, for example, relied upon the Bialer article, which reviewed extended release formulations of anti-epilepsy drugs, including Apydan® Extent, the commercial embodiment of the Franke Patent. Tr. 1206:1-12,

22-25 (Wheless Direct); PTX 555. Apydan® Extent is not approved in the United States, but it was approved in Germany as a twice daily formulation only. Tr. 1206:22-25 (Wheless Direct). The Bialer article describes a phase III clinical trial, in which patients took Apydan® Extent once daily. These patients suffered twice as many seizures as patients taking Trileptal® twice daily. Tr. 1230:19-1231:1 (Wheless Cross).

Jazz and Shire's joint venture to develop an effective once daily oxcarbazepine product also failed after months of experimentation and was eventually terminated due to its failure. See, e.g., Tr. 1634:11-24 (Little Direct); Tr. 57:23-60:13 (Bhatt Direct). While the Court considers this in its analysis, it is not determinative. The Defendants aptly note that "Jazz may have paid the bills, but Drs. Bhatt and Kidane [the inventors on the Patents-in-Suit] did the formulation work." Defendants' Responsive Post-Trial Brief ("Defs. Resp. Br.") at 18 [Docket No. 404]. As such, this is not particularly probative of failure of others. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 759 (N.D. W.Va. 2004) aff'd, 161 F. App'x 944 (Fed. Cir. 2005).

It is clear, though, that Actavis also attempted to develop many different extended release formulations of oxcarbazepine before arriving at the present accused tablets over the course of several years. See, e.g., Tr. 1641:18-1642:7, 1643:14-1651:8

(Little Direct); PTX 72.12-14, 26-28; PTX 74.27-28; PTX 76.27-28. Certain of these formulations, for example, included the element 1(d) release promoting agent only in the coating of the tablet. Tr. 1645:16-1648:21 (Little Direct); PTX 72.26-28; PTX 76.27-28. These formulations, however, were deemed as failures as they did not pass bioequivalence testing. Tr. 1641:18-1651:8 (Little Direct); PTX 351.1.[25]

The Court finds that the record indicates that others had previously failed to develop an effective once daily oxcarbazepine formulation and, as such, supports a finding of non-obviousness.

(4) Surprising and Unexpected Results

"[U]nexpected results can, in appropriate circumstances, be sufficient standing alone to preclude a finding of obviousness." Par Pharm., Inc. v. TWi Pharm., Inc., 773 F.3d 1186, 1200 (Fed. Cir. 2014). The Plaintiff relies nearly exclusively upon the testimony of Dr. Wheless regarding surprising and unexpected results.

[25] Supernus also urges the Court to consider evidence of copying as an indicia of non-obviousness. As the Defendants and the Federal Circuit repeatedly point out, however, "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013) (citing Purdue Pharma Prods. L.P. v. Par Pharm., Inc., 377 F. App'x 978, 983 (Fed. Cir. 2010)).

Based upon his own experience as a neurologist and epileptologist, Dr. Wheless testified that Oxtellar XR® exhibits surprising and unexpected results. Tr. 1207:14-23 (Wheless Direct). His patients have reported "that they were dramatically better on [Oxtellar XR®] from both a side effects standpoint and efficacy standpoint." Id. at 1207:16-18. Dr. Wheless has heard similar accounts from other physicians across the country. Id. at 1207:19-23, 1208:5-9. Dr. Wheless also testified regarding testimonials received by Supernus from patients and physicians that documented patients achieving seizure freedom on Oxtellar XR® despite having long-standing epilepsy and not having achieved seizure freedom on other anti-epileptic drugs. Id. at 1208:10-23.

Actavis challenges Supernus by arguing that the benefits of Oxtellar XR®, to the extent they exist, are not surprising or unexpected. See Defs. Br. at 28-29. Dr. Wheless testified that prior to Supernus's invention, immediate release oxcarbazepine was known to have "fewer drug interactions because it was metabolized differently in the body and it also had fewer side effects," when compared to carbamazepine. Tr. 1190:13-17 (Wheless Direct). The fact that extended release oxcarbazepine would exhibit similar properties is neither surprising nor unexpected.

The record additionally supports Actavis's position that it was known that extended release formulations of any drug generally have a lower incidence of side effects compared with an immediate release formulation of the same drug. Dr. Wheless explained that, after the release of immediate release oxcarbazepine, the "next obvious kind of thought" was to develop an extended release oxcarbazepine as that "should improve the side effects, even more the tolerable [sic], allow us to use this molecule better, if you will, and it will also improve adherence." Id. at 1190:18-24. Dr. Hopfenberg also testified that it was known that controlled or extended release formulations, generally speaking, have better side effect profiles than immediate release drugs. Tr. 1437:13-1438:20 (Hopfenberg Direct). Dr. Fred Lado, Actavis's expert neurologist, also testified that fewer side effects are "exactly why we formulate medications into an extended release" in the first place and, therefore, "that's entirely the expected result." Tr. 1257:15-1258:4 (Lado Direct).

The Court is not persuaded that Oxtellar XR® exhibited surprising and unexpected results and this factor does not support a finding of non-obviousness.

(5) Industry Praise

"Praise and industry acceptance provide additional evidence of nonobviousness." Janssen Products, L.P. v. Lupin Ltd., 109

F. Supp. 3d 650, 671 (D.N.J. 2014) (citing Power-One, Inc. v. Artesyn Techs., Inc., 599 F.3d 1343, 1352 (Fed. Cir. 2010) and Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1574 (Fed. Cir. 1996). Supernus relies upon the testimony of Dr. Wheless and a survey of physicians who prescribed Oxtellar XR® to establish industry praise and acceptance.

Dr. Wheless testified that, based upon his experience as a neurologist treating patients with epilepsy and testimonials received by Supernus, he believes Oxtellar XR® has received industry praise and professional approval. Tr. 1210:6-1211:14 (Wheless Direct). He additionally relied upon a survey of physicians who have prescribed Oxtellar XR®, conducted by Supernus, to come to this conclusion. Id. at 1210:9-10; PTX 409.24-25.

According to this survey, 35% of doctors who had previously prescribed Oxtellar XR® were "somewhat likely" to recommend it to their colleagues, whereas 46% were "very likely" and 13% were "extremely likely" to recommend it. PTX 409.24. None of these doctors reported that they would not recommend Oxtellar XR® to their colleagues and 6% reported they were "not too likely" to recommend it. Id. Of the 71 physicians in the survey who had prescribed Oxtellar XR®, 42% reported that a major factor in their decision to prescribe Oxtellar XR® was that it was a

"significant improvement over immediate-release" oxcarbazepine. PTX 409.25. This was a minor factor for an additional 52%. Id.

The results of the survey indicate at least some praise and acceptance in the industry. The Court, however, affords little weight to the survey since there is no evidence in the record that it has been validated.[26] Additionally, the survey only polled 150 physicians who had received at least one sales call from Supernus. What's more, the figures outlined above only include the responses of the 71 physicians who reported having prescribed Oxtellar. It is not clear to the Court whether this is a sufficient sample size from which to draw any meaningful conclusions. Even if the Court were to credit the survey, it makes clear that only 47% of the 150 physicians who received Oxtellar XR® sales calls actually prescribed the drug. PTX 409.16. Supernus's own records indicate that only 21% of physicians who received Oxtellar XR® sales calls went on to prescribe Oxtellar XR®. PTX 409.20. This is not suggestive of industry praise and acceptance.

[26] Supernus argues that its survey is reliable as it was "conducted by a global market research firm outside the context of this case." Pl. Resp. Br. at 22. This alone is not evidence of its validity. Regardless, the survey remains one commissioned by Supernus for use in its board presentation and the Court does not find it to be particularly persuasive evidence of industry praise and acceptance. See Bayer Healthcare Pharms., Inc. v. Watson, Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013) ("self-referential commendation fall[s] well short of demonstrating true industry praise.").

While the Court found Dr. Wheless to be quite credible and persuasive, his praise and acceptance of Oxtellar XR® is insufficient to carry this factor for Supernus. Accordingly, the Court finds that Supernus has not sufficiently established this indicia of non-obviousness.

(6) Commercial Success

"Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." Merck & Co., Inc. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1376 (Fed. Cir. 2005). Evidence of commercial success is probative of non-obviousness where there is "some causal relation or 'nexus'" between the invention and the commercial success of the invention's commercial embodiment. Id. Supernus relied largely on the testimony of Victor Vaughn, its VP of Sales and Marketing, and Dr. Gordon Rausser, its expert economist, to establish this factor.

The evidence shows that the number of Oxtellar XR® prescriptions is growing over time, Tr. 176:15-177:9 (Vaughn Direct), and that, on a launch-aligned basis, Oxtellar XR® "performed as well if not better than" most other AEDs. Id. at 178:1-6. The net product sales of Oxtellar XR® for the fourth quarter of 2014 were approximately $7.6 million, according to Mr. Vaughn. For that same period, the estimated profitability

of Oxtellar XR® was around $1.2 million. Id. at 191:12-17. Mr. Vaughn testified that Oxtellar XR® was "clearly profitable for the year, first full year of launch for 2014." Id. at 187:14-18.

Dr. David Blackburn, Actavis's expert economist, however, interpreted Oxtellar XR®'s sales figures differently. He testified that Oxtellar XR®'s sales levels "[a]re relatively low. They're low for a pharmaceutical product. The level of prescriptions are low. And on top of being at a low level, they are not growing at a rate that would cause anyone to project substantial sales in the future." Tr. 1743:9-16 (Blackburn Direct). Additionally, the approximately 7,000 prescriptions per month that Oxtellar XR® has earned in the two years since its launch "is not a substantial level of prescriptions" compared to other AEDs on the market, in Dr. Blackburn's opinion. Id. at 1744:25-1745:5; DTX 201 at SUP-OXT00817437. Dr. Blackburn concluded that Oxtellar XR®'s "level of sales is not something that stands out in the AED space. . . . it's not a number indicative of success." Tr. 1746:17-21 (Blackburn Direct).

There is also a dispute as to Oxtellar XR®'s market share. Dr. Rausser testified that Oxtellar XR® was commercially successful as, within two years, it "was able to capture 34 percent of the total branded molecule [oxcarbazepine] for which there were prescriptions written. . . . In other words, it is

capturing a material proportion of what is available to Oxtellar XR® on the market." Tr. 1538:19-25 (Rausser Direct).

Actavis, however, challenges the credibility of Dr. Rausser's analysis. In Actavis's view, Dr. Rausser's analysis is based on the fundamentally flawed premise that the relevant market for Oxtellar XR® is branded oxcarbazepine alone, as opposed to all prescriptions for oxcarbazepine. Defs. Br. at 30. This ignores the generic oxcarbazepine drugs which make up the vast majority of oxcarbazepine prescriptions. Defs. Resp. Br. at 20. The Court is persuaded by Actavis's position. Even Supernus's internal documents describe Oxtellar XR®'s market share after two years as 2.3% of the relevant market, suggesting that Supernus views the relevant market to include all oxcarbazepine prescriptions. See DTX 201 at SUP-OXT00817432. Mr. Vaughn likewise testified that Supernus's objective was to "convert oxcarbazepine to Oxtellar XR®." Tr. 255:9-13 (Vaughn Cross). Mr. Vaughn does not limit the objective to conversion of only branded oxcarbazepine prescriptions, namely those for Trileptal®, to Oxtellar XR®, as that would exclude the vast majority of oxcarbazepine prescriptions.

The Court views this evidence in the context of the AED market. Dr. Rausser explained that there are economic barriers to entering the AED market given doctors' reluctance to changing a patient's medication unless their seizures are poorly

controlled. Tr. 1514:1-6, 1517:19-1519:1; 1539:11-12 (Rausser Direct). Doctors are even reluctant to change a patient to a different version of the same molecule, for example from immediate release oxcarbazepine to extended release oxcarbazepine. Id. at 1518:19-22. Indeed, Dr. Lado, Actavis's expert neurologist, confirmed that "patients and doctors tend to be fairly conservative in changing medications when they have seizure control." Tr. 1257:4-5 (Lado Direct); see also Tr. 170:9-15 (Vaughn Direct) ("Keep in mind epilepsy is a very serious disorder. When a patient has a breakthrough seizure it has devastating effects on that patient, as well as the family. . . . so for that reason physicians are very hesitant to switch a patient from one products [sic] to another.").

In sum, the evidence demonstrates that Oxtellar XR® has been neither a "blockbuster success," as Supernus contends, nor a "lackluster product," as Actavis intimates. It has captured only a small portion of the oxcarbazepine market thus far. However, it has performed adequately compared to its competitors, especially in light of the barriers to entry in the AED market; moreover, it has achieved some degree of profitability in its roughly two years on the market. Ultimately, the Court finds that this factor is neutral.

d) Conclusions of Law

After carefully considering the Graham factors, the Court concludes that Claim 1 of the Patents-in-Suit is valid and would not have been obvious to a person of ordinary skill in the art in 2007. The prior art did not disclose all of the elements of the invention and the Defendants have not provided the Court with sufficient evidence to establish that a person of ordinary skill in the art would have had a motivation to combine the prior art references with a reasonable expectation of success. Therefore, Actavis has failed to rebut the presumption of validity by establishing by clear and convincing evidence that the Patents-in-Suit are invalid as obvious.[27]

The dependent claims likewise are valid, as they depend upon an independent claim that is valid. Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd., 2011 WL 4527353, at *5 (W.D. Pa. Sept. 28, 2011) (citing Wahpeton Canvas Co., Inc. v. Frontier, Inc., 870 F.2d 1546, 1552 n. 9 (Fed. Cir. 1989)) ("Therefore, if a dependent claim depends upon an independent claim that is held valid, the dependent claim must also be valid as at least one of its elements necessarily is not anticipated by the prior art.").

[27] Nonetheless, the Court has evaluated the secondary considerations. As a whole, the Court considers the secondary considerations to be neutral on the record before it.

2. Written Description

Actavis contends that the Patents-in-Suit are invalid for lack of a written description of a homogeneous matrix. Actavis also argues that the '600 Patent is invalid for lack of a written description of the *in vitro* dissolution limitations in Claim 1.

In pertinent part, 35 U.S.C. § 112 provides:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Pursuant to 35 U.S.C. § 112, a patentee must provide a written description that allows a person of ordinary skill in the art to recognize that the patentee invented what is claimed. "The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the [invention] as described in the patent specification." Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345 (Fed. Cir. 2010).

In order to satisfy the written description test, the application must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Ariad Pharms., Inc. v. Eli Lilly

& Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010); Centocor Ortho Biotech, Inc. v. Abbott Labs, 636 F.3d 1341, 1348 (Fed. Cir. 2011). The "level of detail required . . . varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." Ariad Pharms., 598 F.3d at 1351.

Actavis makes two arguments as to its written description defense. First, it argues that the "homogeneous matrix" limitation was not described in the Patents-in-Suit. Specifically, Actavis argues, the specification describes just the structure formed by the matrix polymer when it is fully hydrated and in a state of equilibrium and does not include the other ingredients – the drug, solubility enhancer, and pH-dependent polymer – of the formulation, the focus being the state of the medication during its intended use. Actavis argues that this description is different from the way it was used in the claims. Further, Actavis characterizes the working example recited in the specification as a "superficial" one and contends that a person skilled in the art would not conclude that a tablet in which all ingredients were uniformly dispersed was made. Defs. Br. at 32-33. The Court disagrees.

The specification and prosecution history convey to persons of ordinary skill in the art that, as of the filing dates, Supernus was in possession of the claimed invention. Example 4

explicitly (not superficially) discloses the step by step manufacturing process used by the inventors to produce a homogeneous matrix tablet. See Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-66 (Fed. Cir. 1991) (drawing must convey with reasonable clarity that applicant was in possession of the later-claimed invention including all the limitations and elements). Indeed, as the prosecution history demonstrates, the inventors amended Claim 1 to recite a homogeneous matrix derived according to the protocols set forth in the examples of the Patents-in-Suit. PTX 5.298; Tr. 613:12-614:22 (Little Direct). In the high shear granulation manufacturing process disclosed in Example 4, all of the ingredients except for magnesium stearate – oxcarbazepine, Prosolv SMC C50, PVP K25, HPMC K4M, and Eudragit L100-55 - are mixed together. See ’898 Patent, col. 4, ll. 40-42; see also Tr. 464:16-22 (Kidane Depo).

Indeed, Actavis’s expert, Dr. Hopfenberg, agreed on cross-examination that a person of skill in the art making a matrix tablet would be able to create a homogeneous matrix formulation:

> Q. Would you agree that absent a specific objective not to be homogeneous, the default objective for a pharmaceutical formulator would be to create a homogeneous matrix formulation that would comprise a uniform dispersion of ingredients?
>
> A. I think that would be an obvious objective of the skilled formulator.
>
> Q. So you would agree with that statement?

A. I would.

Q. You would also agree that the objective of the person of ordinary skill in the art forming such a matrix device would be to form a homogeneous matrix in the absence of any disclaimer to the contrary. Do you agree with that statement?

A. I believe I would give the same answer I did before, the person of ordinary skill in the art formulating a matrix-based formulation -- the person of ordinary skill in the art developing a matrix-based formulation would have as an objective the formation of a homogeneous matrix.

Q. And you would agree, finally, Dr. Hopfenberg, that there can still be a resulting homogeneous matrix if some ingredients are added before granulation and some ingredients are added after granulation, correct?

A. I think anything is possible, but the -- that's possible.

Tr. 1493:12-1494:9 (Hopfenberg Cross).

Actavis argues that Supernus's reliance upon Dr. Hopfenberg's testimony is misplaced because Dr. Hopfenberg simply described in general terms what a person skilled in the art would like to achieve in a formulation, that is, a homogeneous matrix, and not the invention. This Court disagrees. The specification sets forth the manufacturing process in Example 4 how to produce a homogeneous matrix. When the term "homogeneous matrix" was added to the claim to address the Examiner's concerns, the applicants stated that "one of ordinary skill in the art would appreciate that the formulations derived according to the protocol set forth in the Examples

would necessarily comprise a homogeneous matrix." PTX 5.298. This is the "descriptive matter" that goes beyond simply describing the prior art as Actavis argues. Cf. Tronzo v. Biomet, Inc., 156 F.3d 1154, 1159 (Fed. Cir. 1998) (simply describing prior art does not meet the written description requirement).

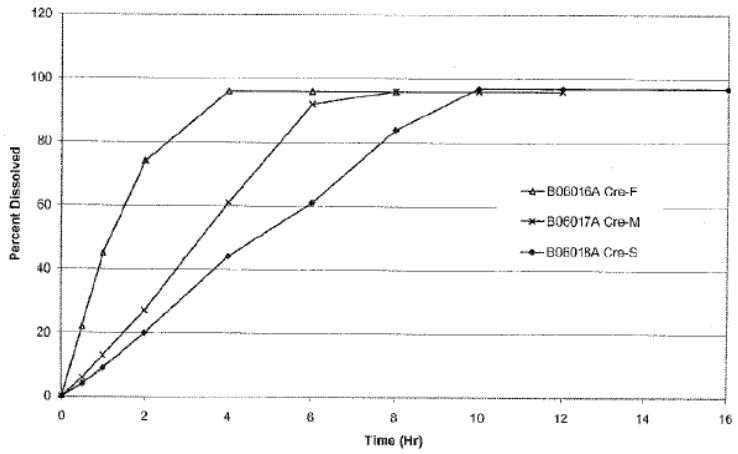
The Court now turns to Actavis's argument regarding the '600 Patent, even though it has found no infringement. Claim 1 of the '600 Patent includes the *in vitro* dissolution limitations to the formulation claimed:

> wherein, in vitro:
>
> (i) between 20 and 74% of the total oxcarbazepine is released by 2 hours; and
>
> (ii) between 44 and 96% of the total oxcarbazepine is released by 4 hours.

Actavis acknowledges that the range numbers were selected from Figure 6, with the lower numbers from the bottom curve and the higher numbers from the top curve. DFOF ¶¶ 525-530. The Defendants argue, however, that Supernus impermissively claimed an expansive range by "mixing and matching arbitrary points on dissolution curves of different formulations." Defs. Br. at 33-34; see also DFOF ¶¶ 523-29. Thus, Dr. Hopfenberg testified, a person skilled in the art would not consider the inventors to be in possession of such breadth. Tr. 1399:9-13 (Hopfenberg Direct). The Court disagrees.

The standard for written description does not require an inventor "to reduce to practice and be in physical possession of every species." Pfizer Inc. v. Teva Pharm. USA, Inc., 555 F. App'x 961, 968 (Fed. Cir. 2014). Figure 6 of the Supernus Patents illustrates three exemplary dissolution profiles for the fast (CRe-F), medium (CRe-M), and slow (CRe-S) oxcarbazepine formulations.

FIGURE 6



The '600 Patent states that USP Apparatus II at 60 RPM was used, and the dissolution medium was 1% SLS in water. '600 Patent, col. 3, ll. 24-25. This is sufficient to allow a person skilled in the art to know that the inventors were in possession of at least three formulations with *in vitro* release profiles covered by Claim 1.

3. Indefiniteness

Finally, Actavis argues that the Patents-in-Suit are invalid as indefinite because the specification and prosecution history contain no guidance on how to determine if a matrix is homogeneous. Actavis further argues that the *in vitro* limitations in the '600 Patent are indefinite because they provide no guidance on what set of conditions do or do not control in producing the claimed ranges.

Pursuant to 35 U.S.C. § 112(b), "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention." The Supreme Court has explained that this requirement "entails a 'delicate balance.'" Nautilus, Inc. v. Biosig Instruments, Inc., 134 S. Ct. 2120, 2128 (2014) (quoting Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 731 (2002)). Section 112(b) requires that a patent "be precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them." Id. at 2129 (internal citations and quotations omitted). Nonetheless, it also recognizes "the inherent limitations of language" and permits "[s]ome modicum of uncertainty." Id. at 2128.

In other words, Section 112(b) requires that "a patent's claims, viewed in light of the specification and prosecution

history, inform those skilled in the art about the scope of the invention with reasonable certainty." Id. at 2129. "The definiteness requirement, so understood, mandates clarity, while recognizing that absolute precision is unattainable." Id.

As for the term "homogeneous matrix," Actavis contends that there is nothing in the specification that sets a "clear line" between a matrix that is homogeneous and one that is not. Defs. Br. at 37. To prove its point, Actavis remonstrates that even Dr. Bugay testified that there was no generally recognized standard, including the standard technique of chemical imaging, that could answer the question of whether a distribution of ingredients was uniform or not. Id. Actavis's protestations are actually borne out of its undue emphasis on chemical imaging and eschewal of the understanding of a homogeneous matrix by a person of ordinary skill in the art.

It is clear that persons skilled in the art understood that "homogeneous" means a mixture of two or more ingredients that are uniformly dispersed in a pharmaceutical formulation. Throughout the trial, it was evident that persons skilled in the art understood that homogeneity varied in degrees. As set forth above, both parties' experts agreed. See Tr. 904:8-12 (Muzzio Direct); Tr. 377:1-19 (Bugay Cross). Moreover, persons skilled in the art also understood that perfect homogeneity was not achievable because perfect molecular uniformity in a

pharmaceutical formulation was not possible. Tr. 341:20-23 (Bugay Direct); Tr. 373:3-22 (Bugay Cross). Additionally, as Dr. Little persuasively testified, a person skilled in the art could turn to FDA uniformity testing to confirm that a particular manufacturing process worked as intended. See Tr. 634:14-635:3 (Little Direct). Indeed, Example 4 discloses the manufacturing step by step process the inventors used to produce a homogeneous matrix tablet. As this Court has stated, supra at footnote 14, chemical imaging is a standard that confirms homogeneity, but it is not essential to the Patents-in-Suit to survive an indefiniteness challenge.

As to Claim 1 of the ’600 Patent, although the Court need not reach this issue, the Patent is not indefinite. The ’600 Patent discloses a standard set of dissolution test conditions, to wit, USP Apparatus II, 60 RPM, 1% SLS, that could be implemented by a pharmaceutical formulator.

Accordingly, the Patents-in-Suit are not invalid as indefinite.

IV. CONCLUSION

For the foregoing reasons, the Court finds that the Defendants’ ANDA product will infringe the ’898 Patent and the ’131 Patent. The Court, however, finds that the Defendants’ ANDA product will not infringe the ’600 Patent. The Court additionally finds that all three Patents-in-Suit are valid.

Accordingly, the Court enters judgment in favor of Supernus and against Actavis as to the ’898 Patent and the ’131 Patent, and in favor of Actavis and against Supernus as to the ’600 Patent. Actavis’s oral motion for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c) is GRANTED as to the ’600 Patent. An appropriate Order will issue herewith.

s/Renée Marie Bumb
RENÉE MARIE BUMB
UNITED STATES DISTRICT JUDGE

Dated: February 5, 2016

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SUPERNUS PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ACTAVIS INC., WATSON LABORATORIES, INC. – FLORIDA (N/K/A ACTAVIS LABORATORIES FL, INC.), ACTAVIS PHARMA, INC., WATSON LABORATORIES, INC., and ANDA, INC.,** **Defendants.**	**Civil Action No. 13-4740(RMB)(JS)** **Civil Action No. 14-1981(RMB)(JS)** **(Consolidated)**

~~[PROPOSED]~~ FINAL JUDGMENT

WHEREAS, Plaintiff Supernus Pharmaceuticals, Inc. ("Supernus") asserted that the submission of Abbreviated New Drug Application ("ANDA") No. 205444 by Defendants Actavis Inc., Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Watson Laboratories, Inc., and Anda, Inc. (all of the Defendants are collectively "Actavis," and together with Supernus, the "Parties") for generic oxcarbazepine extended-release tablets, containing 150 mg, 300 mg, and 600 mg of oxcarbazepine ("Actavis's ANDA Products") infringed United States Patent Nos. 7,722,898 ("the '898 patent"), 7,910,131 ("the '131 patent"), and 8,617,600 ("the '600 patent");

WHEREAS, Supernus further asserted that the commercial manufacture, use, offer to sell, sale, or importation of Actavis's ANDA Products, if approved by the United States Food and Drug Administration ("FDA") prior to the expiration of the '898 patent, the '131 patent, and the '600 patent, would infringe those patents;

WHEREAS, this action was tried before the Court on November 18, 19, and 30, and December 1, 2, 3, and 4, and the Court issued its Opinion (D.I. 417 and 418) on February 5, 2016, finding that all of the asserted claims of the '898 patent and the '131 patent were infringed and not invalid, and that the asserted claims of the '600 patent are not infringed and not invalid;

NOW THEREFORE, IT IS HEREBY ORDERED, ADJUDGED, AND DECREED that:

1. This Court has jurisdiction over the Parties and subject matter of this action.

2. Final Judgment is entered in favor of Supernus and against Actavis on all claims and counterclaims with respect to the '898 patent. Actavis's 150 mg product that is the subject of Actavis's ANDA No. 205444 infringes claims 1, 7, 11, 18, and 19 of the '898 patent. Actavis's 300 mg product that is the subject of Actavis's ANDA No. 205444 infringes claims 1, 6, 7, 11, 18, and 19 of the '898 patent. Actavis's 600 mg product that is the subject of Actavis's

ANDA No. 205444 infringes claims 1, 6-8, 11, 18, and 19 of the '898 patent. Claims 1, 6-8, 11, 18, and 19 of the '898 patent are not invalid.

3. Final Judgment is entered in favor of Supernus and against Actavis on all claims and counterclaims with respect to the '131 patent. Actavis's 150 mg product that is the subject of Actavis's ANDA No. 205444 infringes claims 7, 11, 18, 19, and 21 of the '131 patent. Actavis's 300 mg product that is the subject of Actavis's ANDA No. 205444 infringes claims 6-7, 11, 18, 19, and 21 of the '131 patent. Actavis's 600 mg product that is the subject of Actavis's ANDA No. 205444 infringes claims 6-8, 11, 18, 19, and 21 of the '131 patent. Claims 6-8, 11, 18, 19, and 21 of the '131 patent are not invalid.

4. Final Judgment is entered in favor of Actavis and against Supernus on Supernus's infringement claims with respect to the '600 patent. Actavis's ANDA Products do not infringe claims 1, 7-9, 12, 18, or 19 of the '600 patent.

5. Final Judgment is entered in favor of Supernus and against Actavis on Actavis's invalidity counterclaim with respect to the '600 patent. Claims 1, 7-9, 12, 18, and 19 of the '600 patent are not invalid.

6. Pursuant to 35 U.S.C. § 271(e)(4)(A) the effective date of any approval of Actavis's ANDA No. 205444 shall be no earlier than the expiration date of the '898 patent and the '131 patent, including any extensions by FDA.

7. Pursuant to 35 U.S.C. § 271(e)(4)(B) Actavis and its officers, agents, servants, employees, and attorneys, and other persons in active concert or participation with any of them, are hereby enjoined from commercially manufacturing, using, offering to sell, or selling within the United States, or importing into the United States Actavis's ANDA Products until the expiration of the '898 patent and '131 patent, including any extensions by FDA.

8. Actavis shall (i) promptly inform the U.S. Food and Drug Administration of this Final Judgment and that, for ANDA No. 205444, a final judgment has been entered that all of the asserted claims of the '898 patent and the '131 patent are infringed and not invalid; and (ii) provide confirmation of such communication to Supernus within seven days thereof.

9. If any party appeals from this Final Judgment, any Bill of Costs, motion as to prevailing-party status, or motion for attorneys' fees or costs shall be filed and served within thirty days after issuance of the mandate from any such appeal (which filing shall be considered timely); otherwise, if neither party appeals, any Bill of Costs, motion as to prevailing party status, or motion for attorneys' fees or costs shall be considered timely if filed and served within thirty days after the time to file a notice of appeal has expired.

10. All pending motions and other outstanding requests for relief not specifically addressed herein are DENIED.

IT IS SO ORDERED this 18th day of February 2016.

RENÉE MARIE BUMB
United States District Court Judge

(12) **United States Patent**
Bhatt et al.

(10) **Patent No.: US 7,722,898 B2**
(45) **Date of Patent: May 25, 2010**

(54) **MODIFIED-RELEASE PREPARATIONS CONTAINING OXCARBAZEPINE AND DERIVATIVES THEREOF**

(75) Inventors: **Padmanabh P. Bhatt**, Rockville, MD (US); **Argaw Kidane**, Montgomery Village, MD (US); **Kevin Edwards**, Lovettsville, VA (US)

(73) Assignee: **Supernus Pharmaceuticals, Inc.**, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **11/734,874**

(22) Filed: **Apr. 13, 2007**

(65) **Prior Publication Data**

US 2007/0254033 A1 Nov. 1, 2007

Related U.S. Application Data

(60) Provisional application No. 60/794,837, filed on Apr. 26, 2006.

(51) **Int. Cl.**
A61K 9/22 (2006.01)

(52) **U.S. Cl.** **424/468**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner—Michael G Hartley
Assistant Examiner—Paul Dickinson
(74) *Attorney, Agent, or Firm*—Stephen B. Maebius; Sunit Talapatra; Anna Ganelina

(57) **ABSTRACT**

Controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration are disclosed. The inventive compositions comprise solubility-and/or release enhancing agents to provide tailored drug release profiles, preferably sigmoidal release profiles. Methods of treatment comprising the inventive compositions are also disclosed.

20 Claims, 14 Drawing Sheets

FIGURE 1

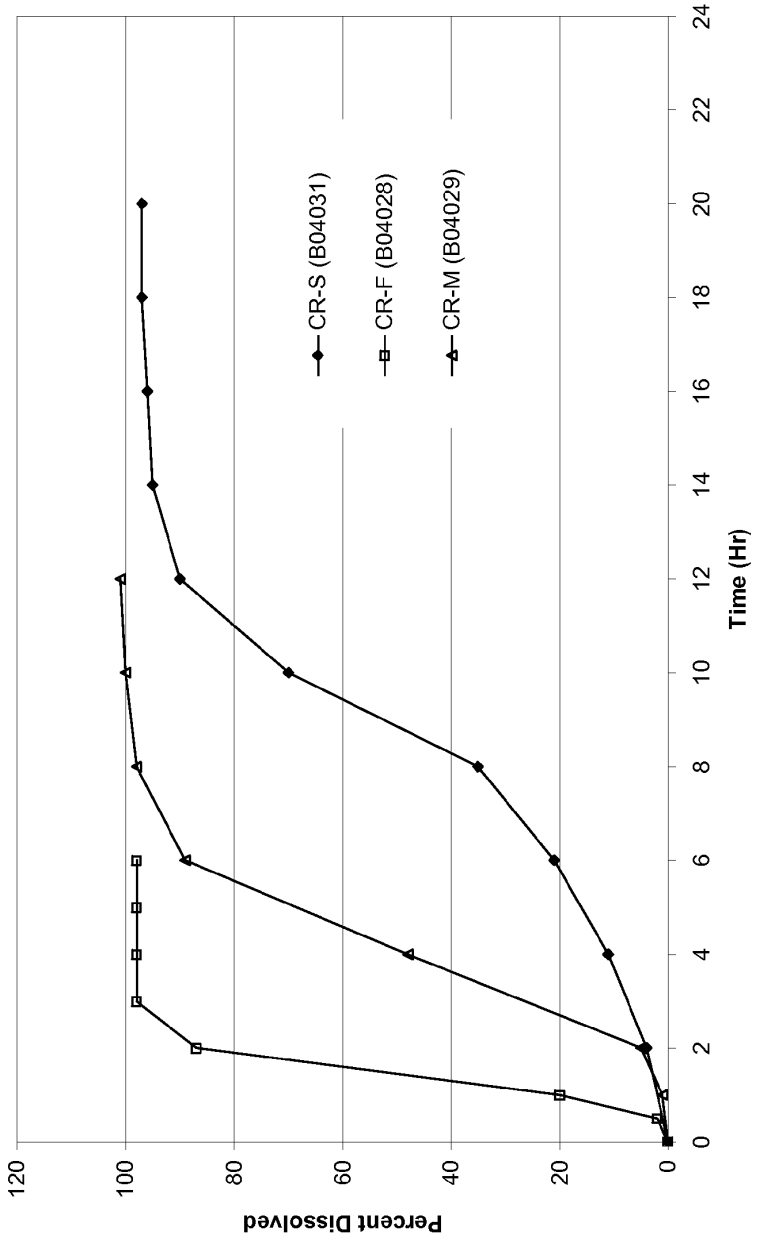

CR-S (B04031)
CR-F (B04028)
CR-M (B04029)
Percent Dissolved
120
100
80
60
40
20
0
Time (Hr)
0
2
4
6
8
10
12
14
16
18
20
22
24

FIGURE 2

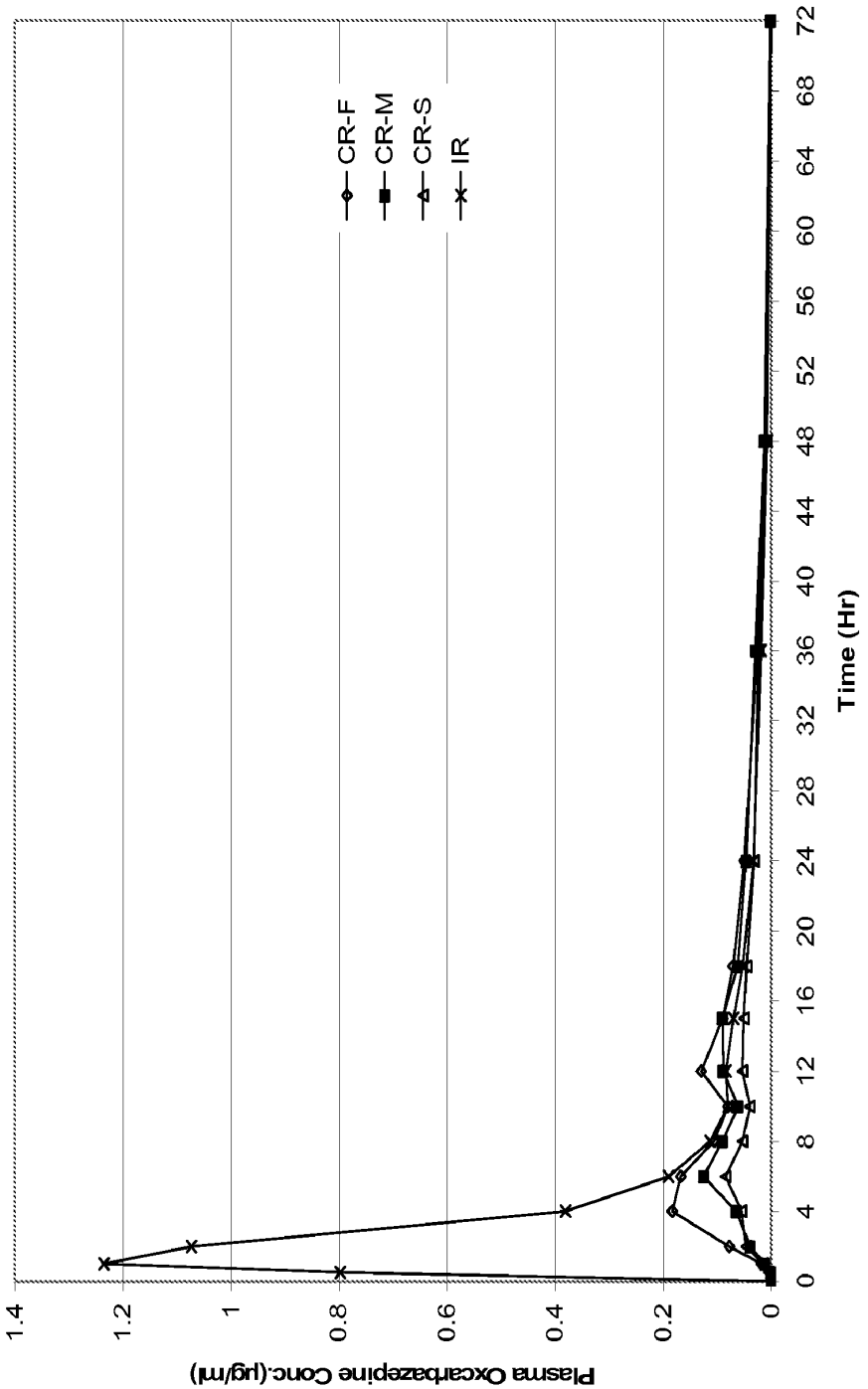

CR-F
CR-M
CR-S
IR
Plasma Oxcarbazepine Conc.(µg/ml)
Time (Hr)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72

FIGURE 3

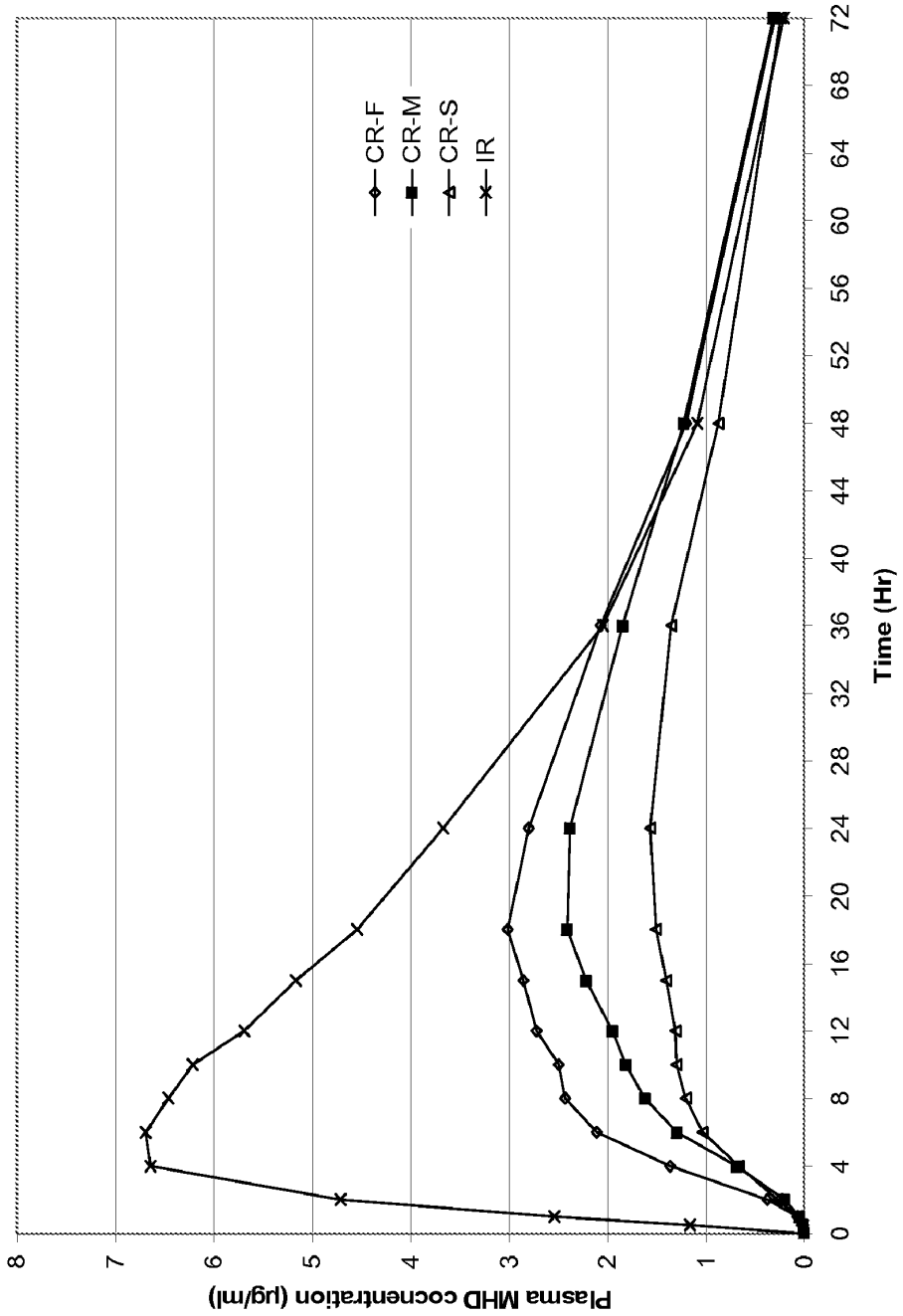

CR-F
CR-M
CR-S
IR
Plasma MHD concentration (µg/ml)
Time (Hr)
0
1
2
3
4
5
6
7
8
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72

FIGURE 4

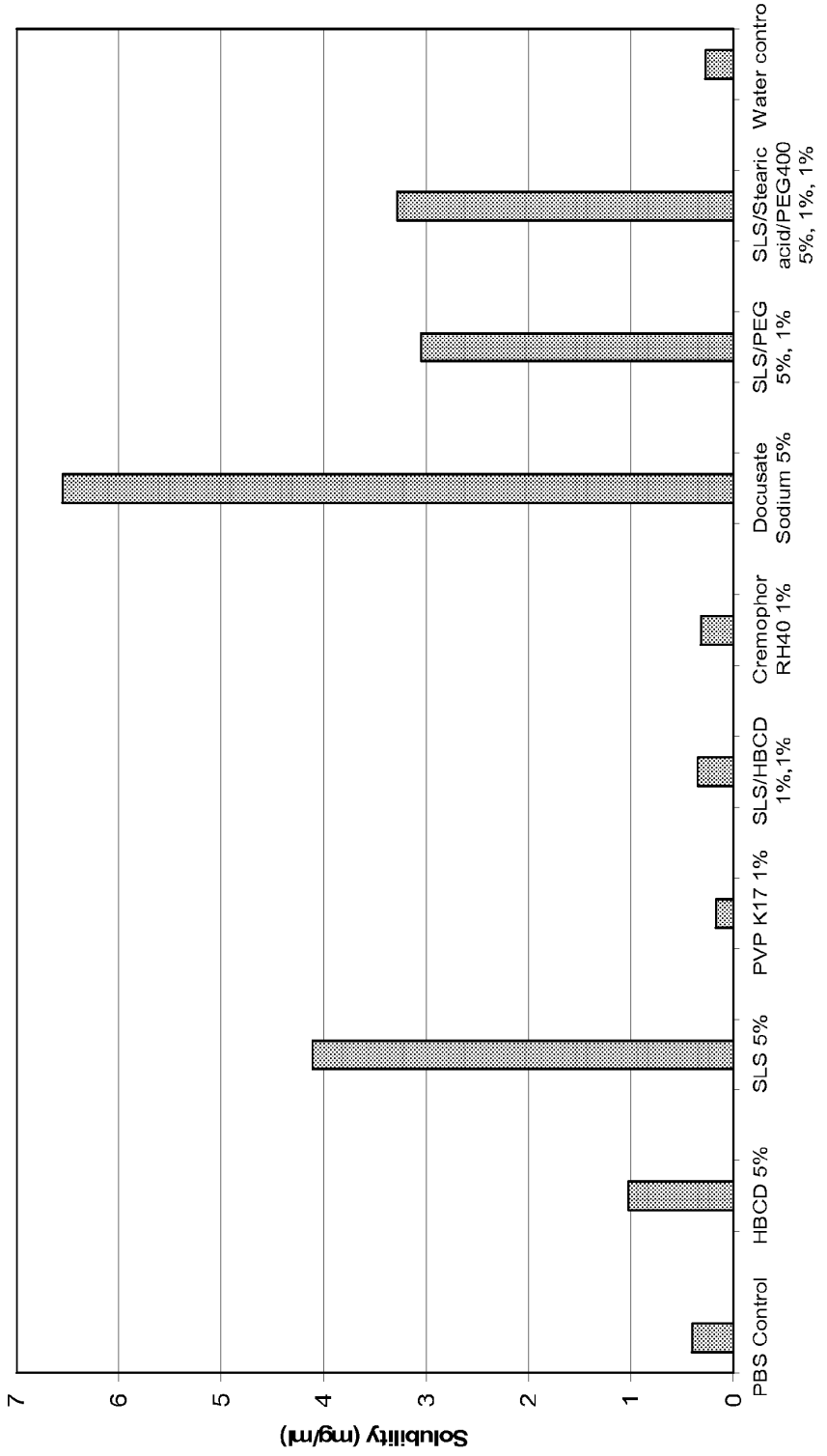

Solubility (mg/ml)
0
1
2
3
4
5
6
7
PBS Control
HBCD 5%
SLS 5%
PVP K17 1%
SLS/HBCD 1%,1%
Cremophor RH40 1%
Docusate Sodium 5%
SLS/PEG 5%, 1%
SLS/Stearic acid/PEG400 5%, 1%, 1%
Water contro

FIGURE 5

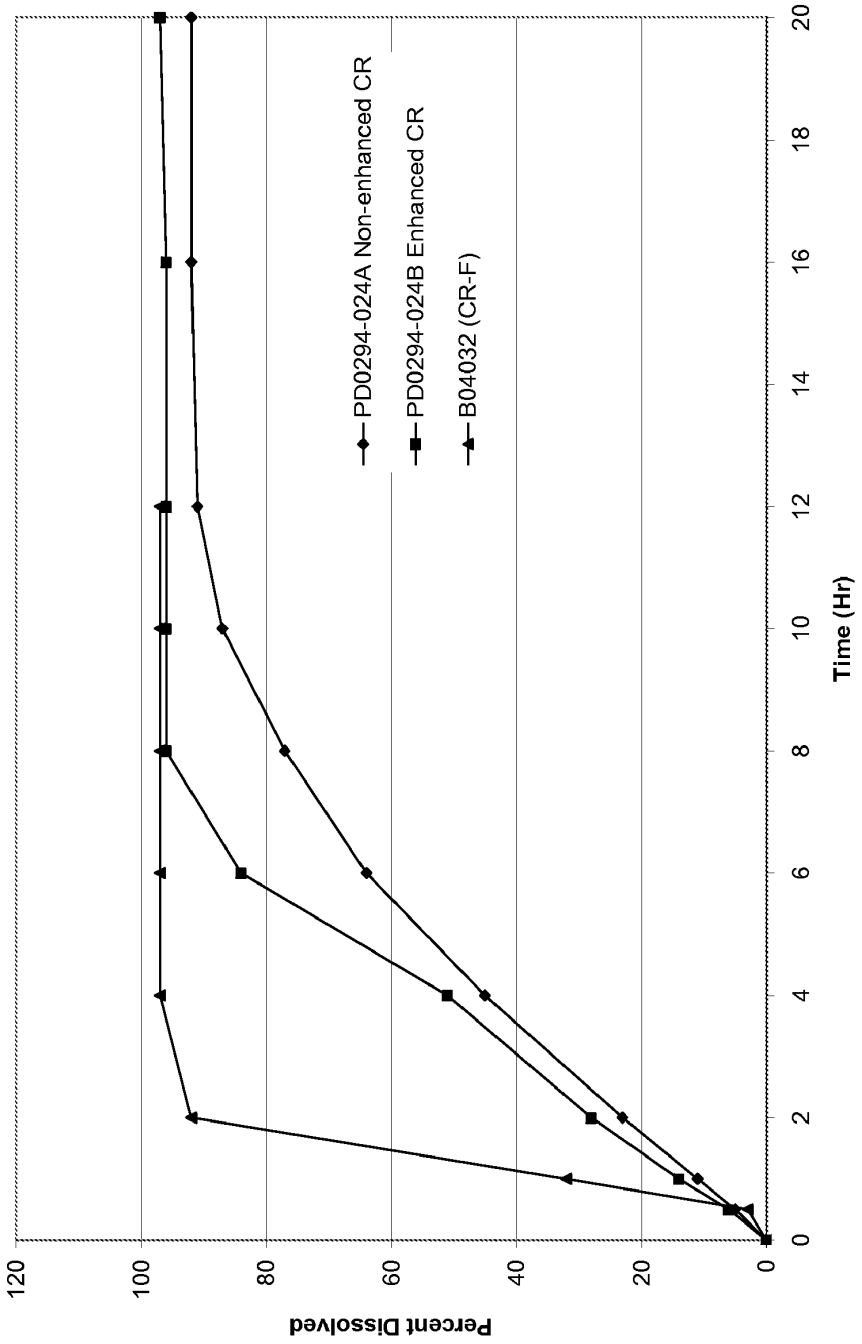

PD0294-024A Non-enhanced CR
PD0294-024B Enhanced CR
B04032 (CR-F)
Percent Dissolved
0
20
40
60
80
100
120
Time (Hr)
0
2
4
6
8
10
12
14
16
18
20

FIGURE 6

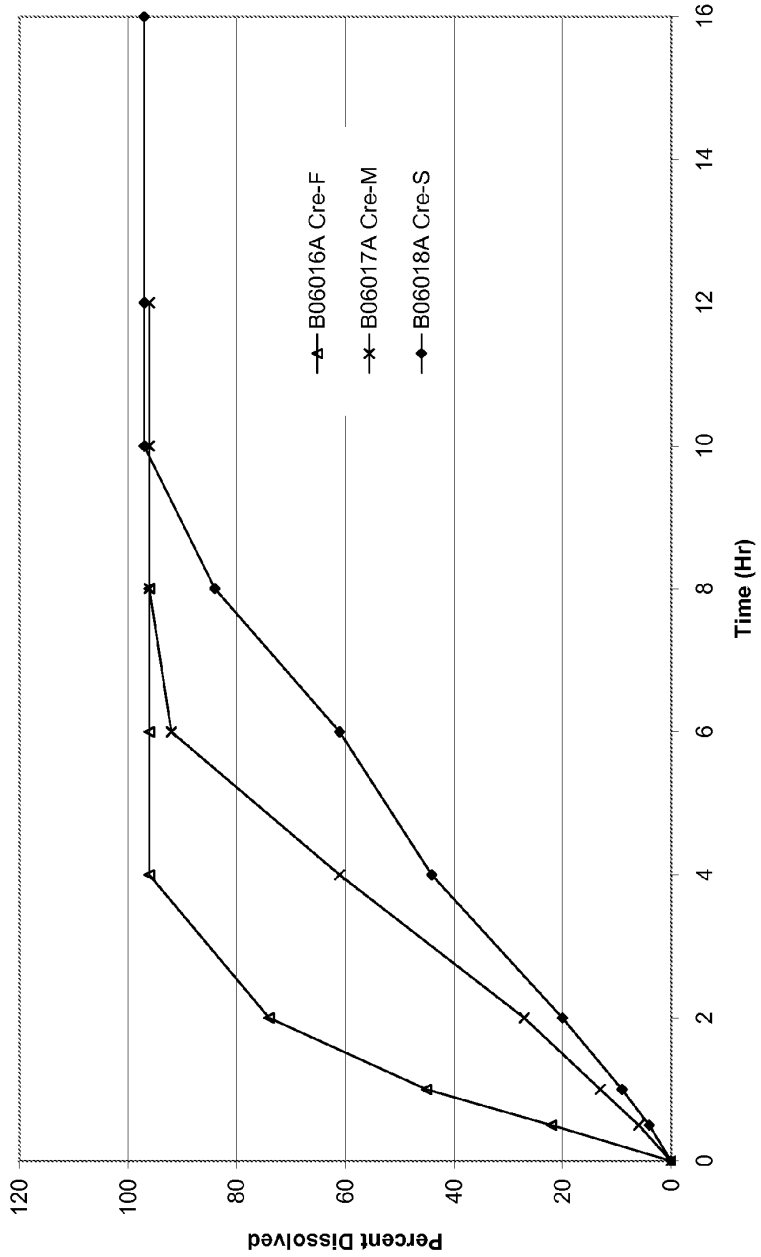

Percent Dissolved
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Time (Hr)
B06016A Cre-F
B06017A Cre-M
B06018A Cre-S

FIGURE 7

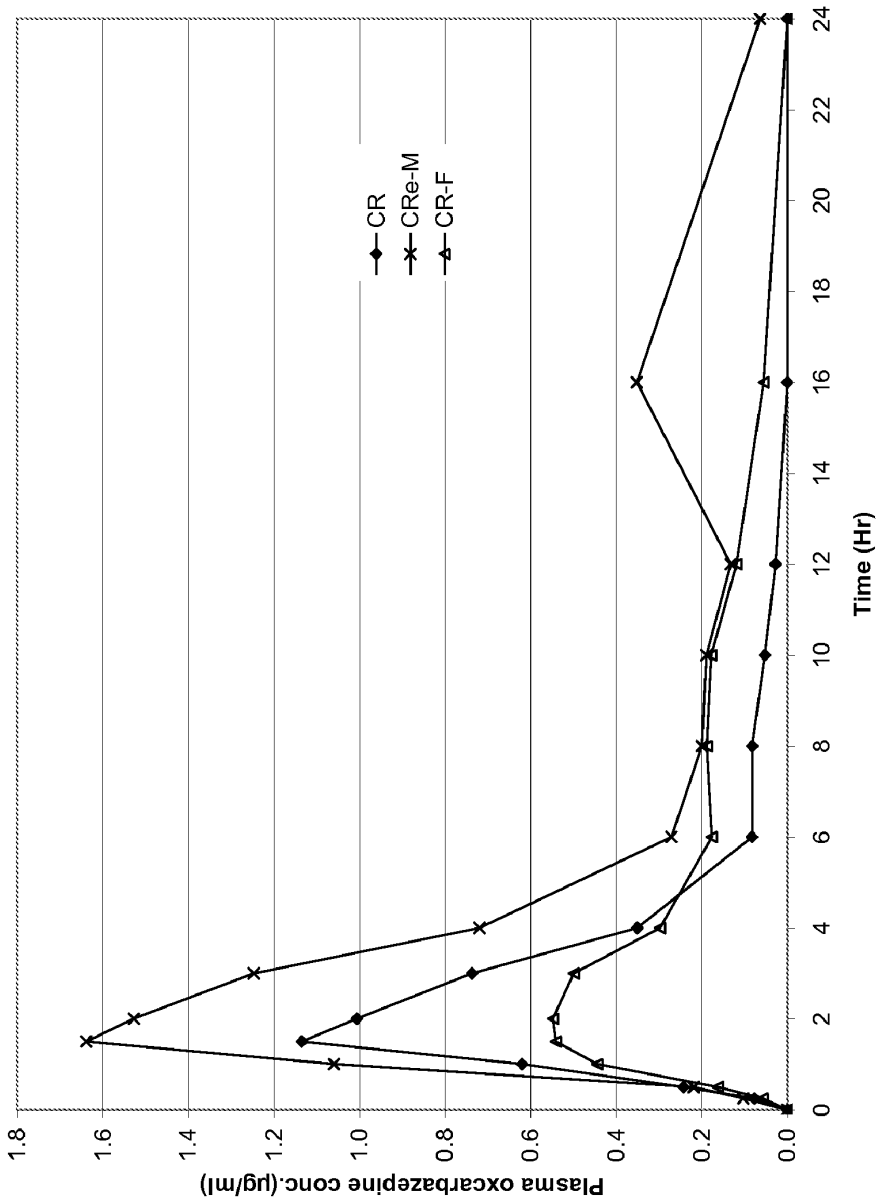

CR
CRe-M
CR-F
Plasma oxcarbazepine conc.(µg/ml)
Time (Hr)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
0
2
4
6
8
10
12
14
16
18
20
22
24

FIGURE 8

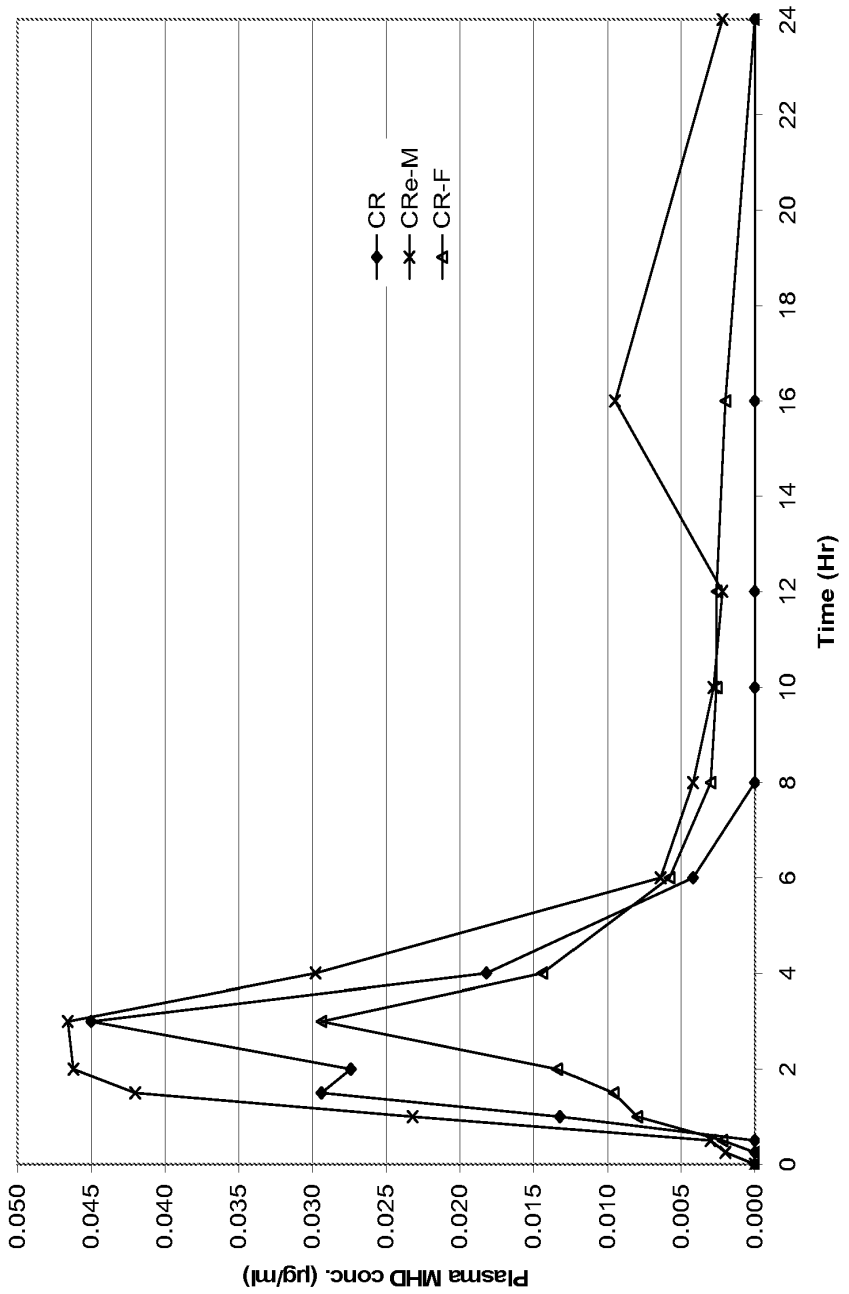

Plasma MHD conc. (µg/ml)
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
Time (Hr)
0
2
4
6
8
10
12
14
16
18
20
22
24
CR
CRe-M
CR-F

FIGURE 9

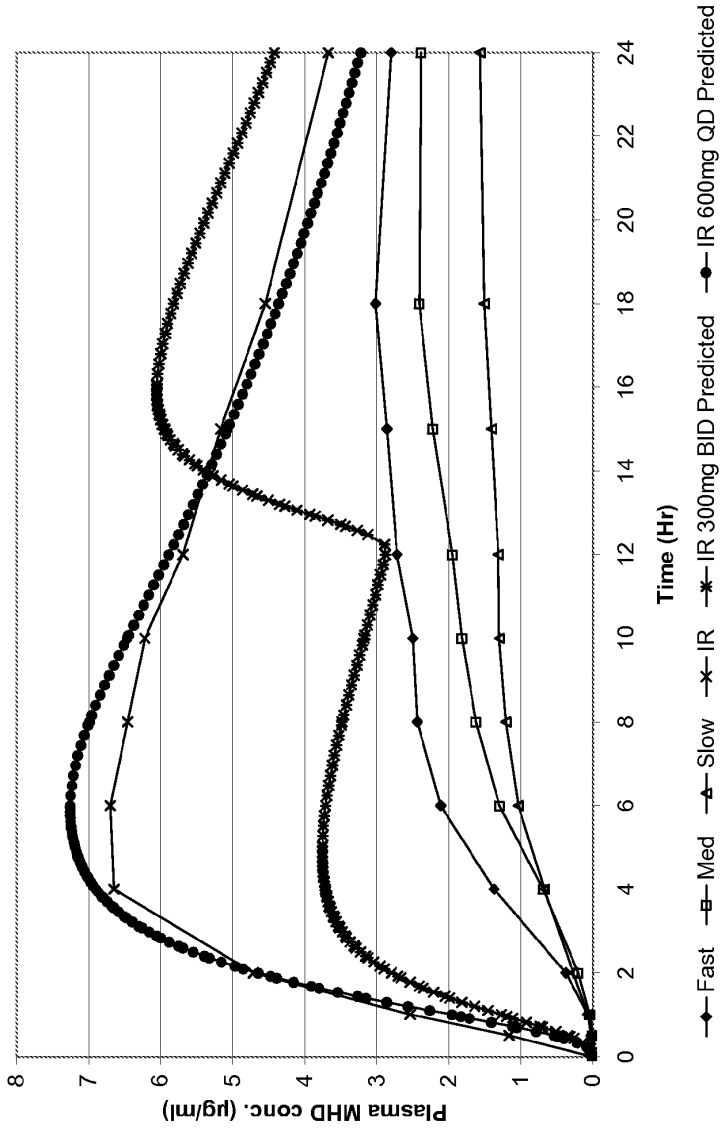

Plasma MHD conc. (µg/ml)
0
1
2
3
4
5
6
7
8
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hr)
Fast
Med
Slow
IR
IR 300mg BID Predicted
IR 600mg QD Predicted

FIGURE 10

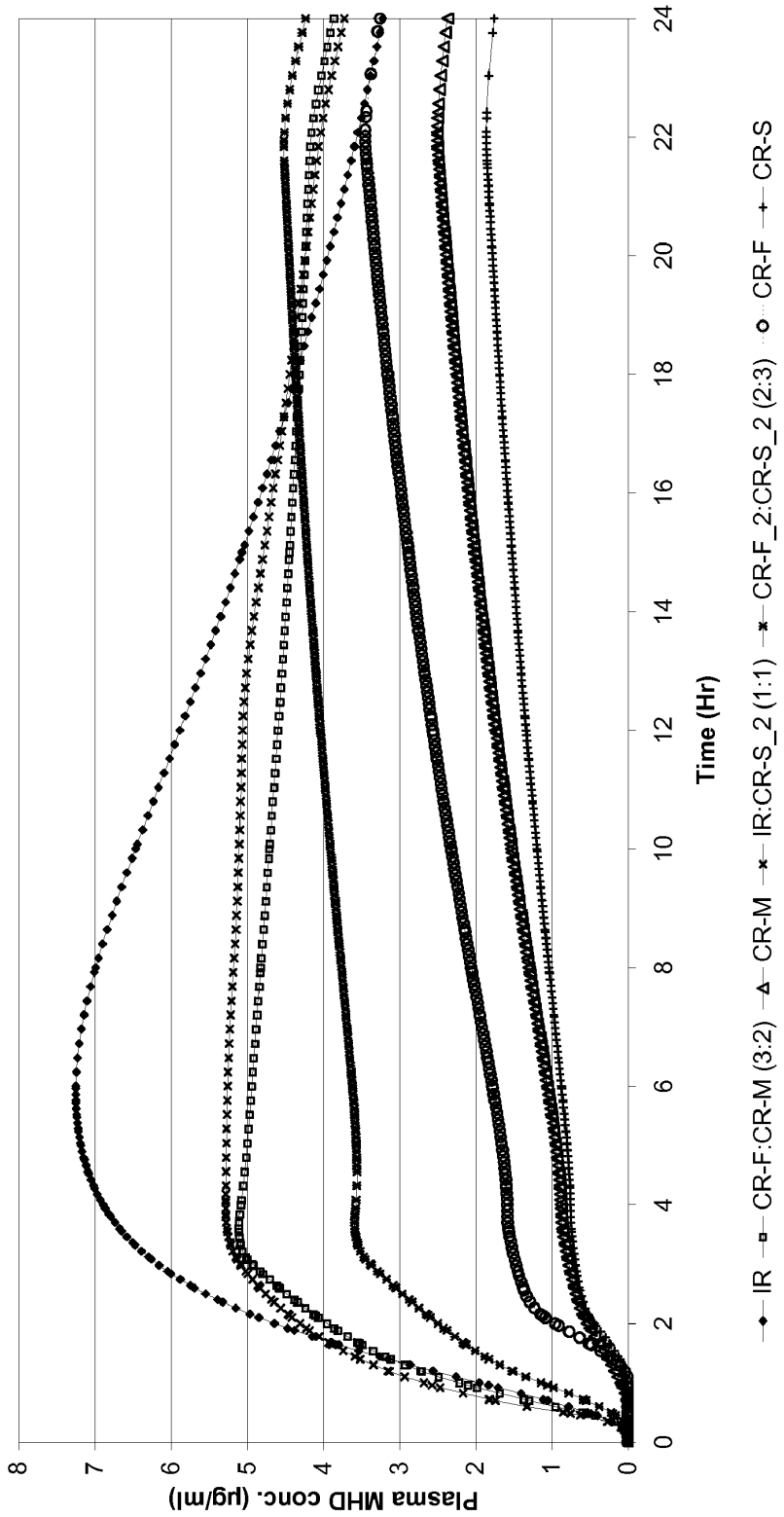

Plasma MHD conc. (µg/ml)
0
1
2
3
4
5
6
7
8
Time (Hr)
0
2
4
6
8
10
12
14
16
18
20
22
24
IR
CR-F:CR-M (3:2)
CR-M
IR:CR-S_2 (1:1)
CR-F_2:CR-S_2 (2:3)
CR-F
CR-S

FIGURE 11

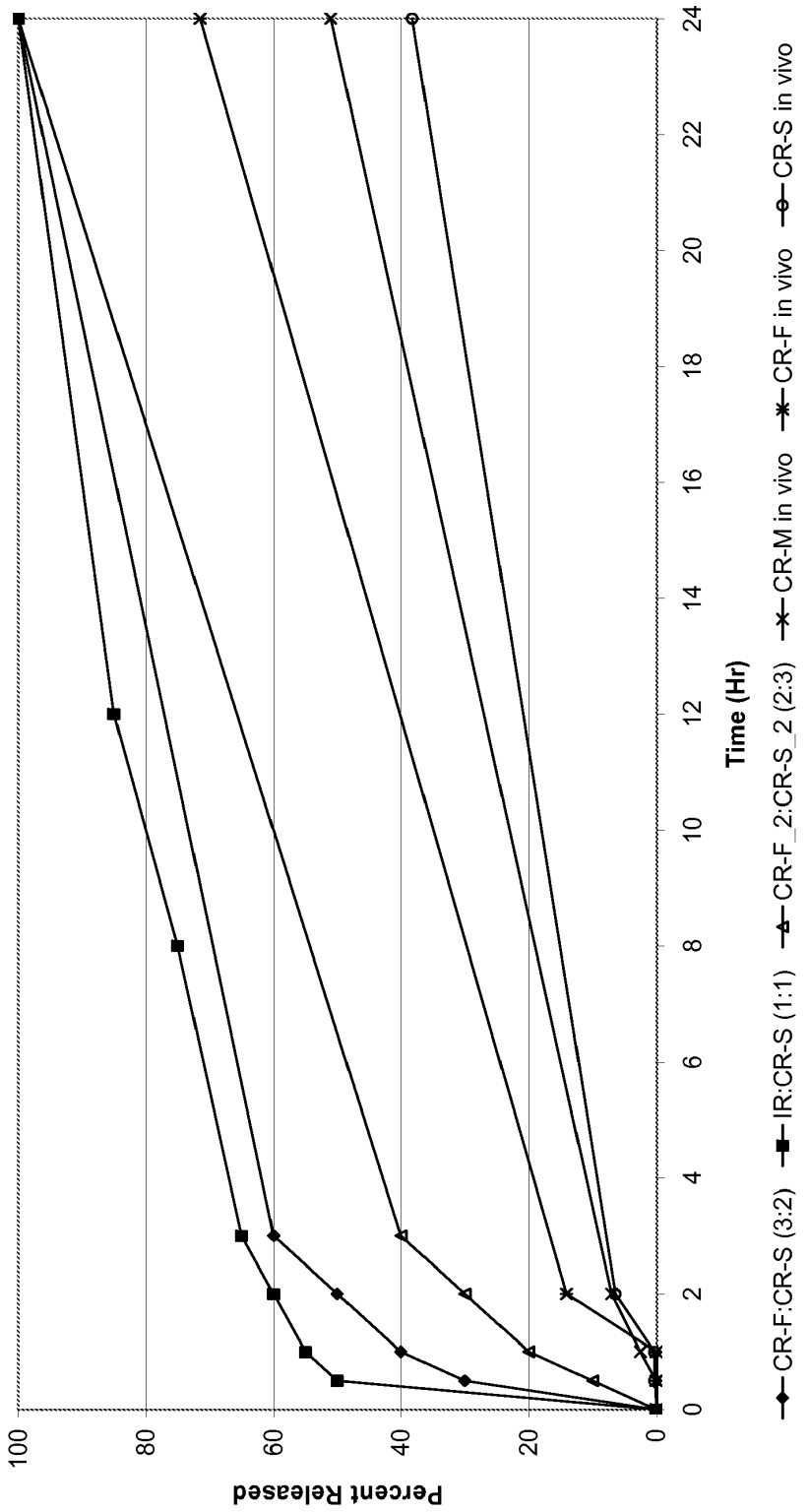

Percent Released
0
20
40
60
80
100
Time (Hr)
0
2
4
6
8
10
12
14
16
18
20
22
24
CR-F:CR-S (3:2)
IR:CR-S (1:1)
CR-F_2:CR-S_2 (2:3)
CR-M in vivo
CR-F in vivo
CR-S in vivo

FIGURE 12

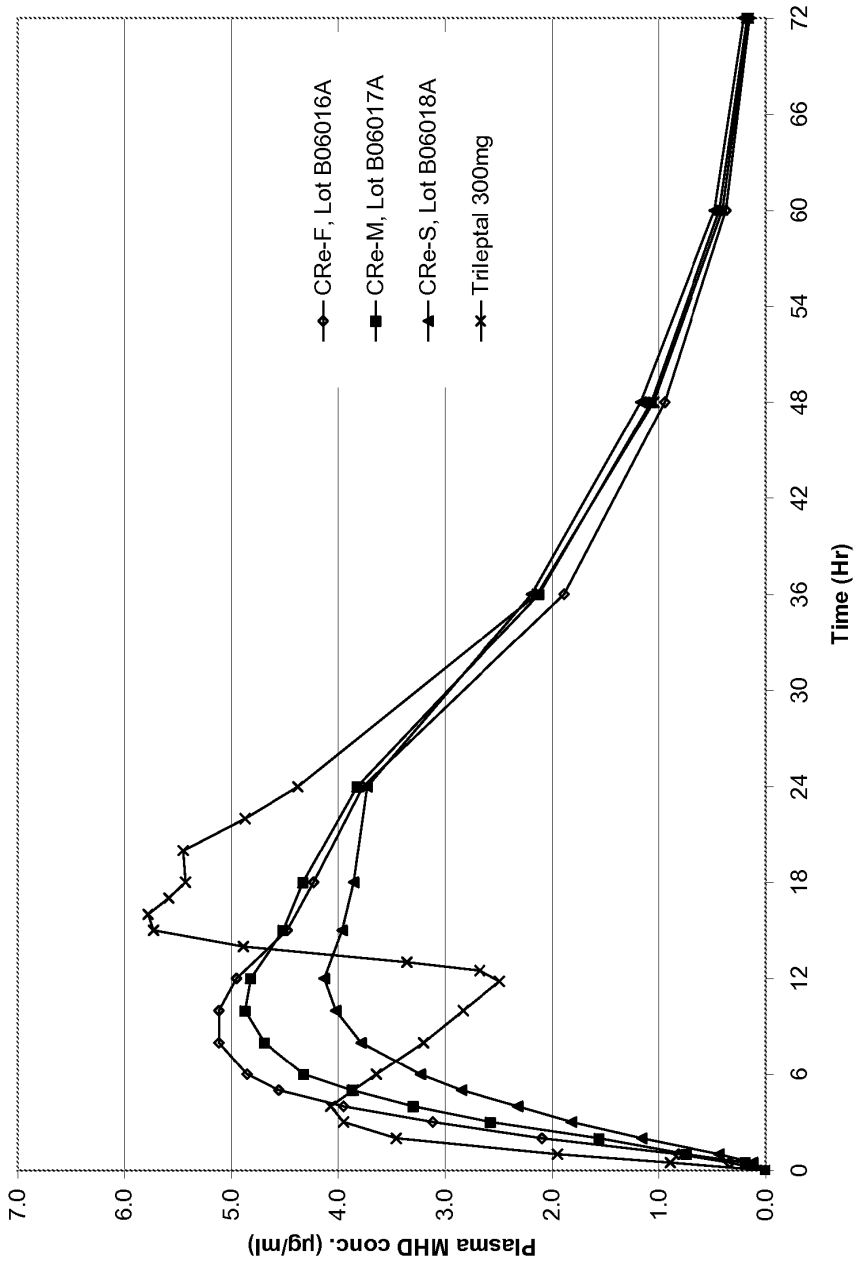

CRe-F, Lot B06016A
CRe-M, Lot B06017A
CRe-S, Lot B06018A
Trileptal 300mg
Plasma MHD conc. (µg/ml)
Time (Hr)
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
0
6
12
18
24
30
36
42
48
54
60
66
72

FIGURE 13

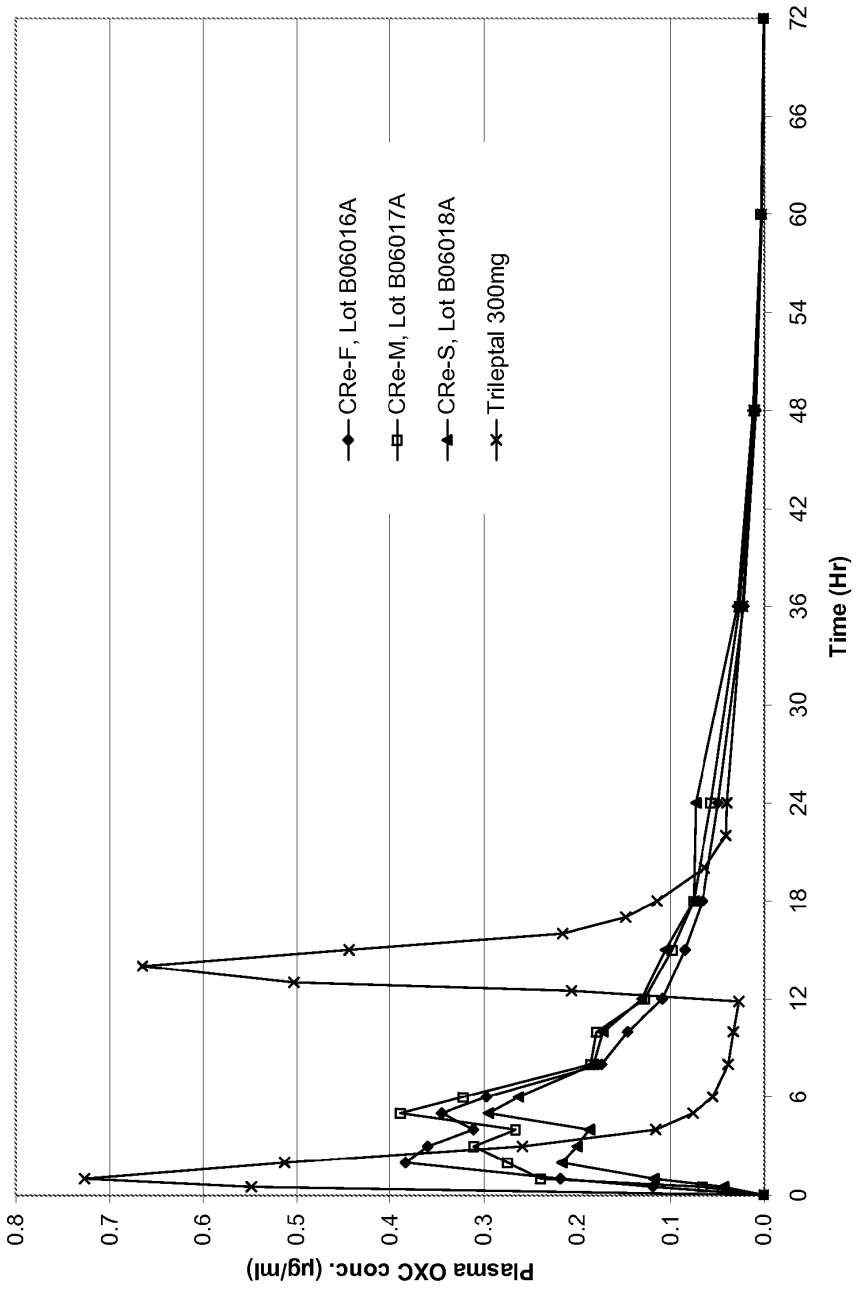
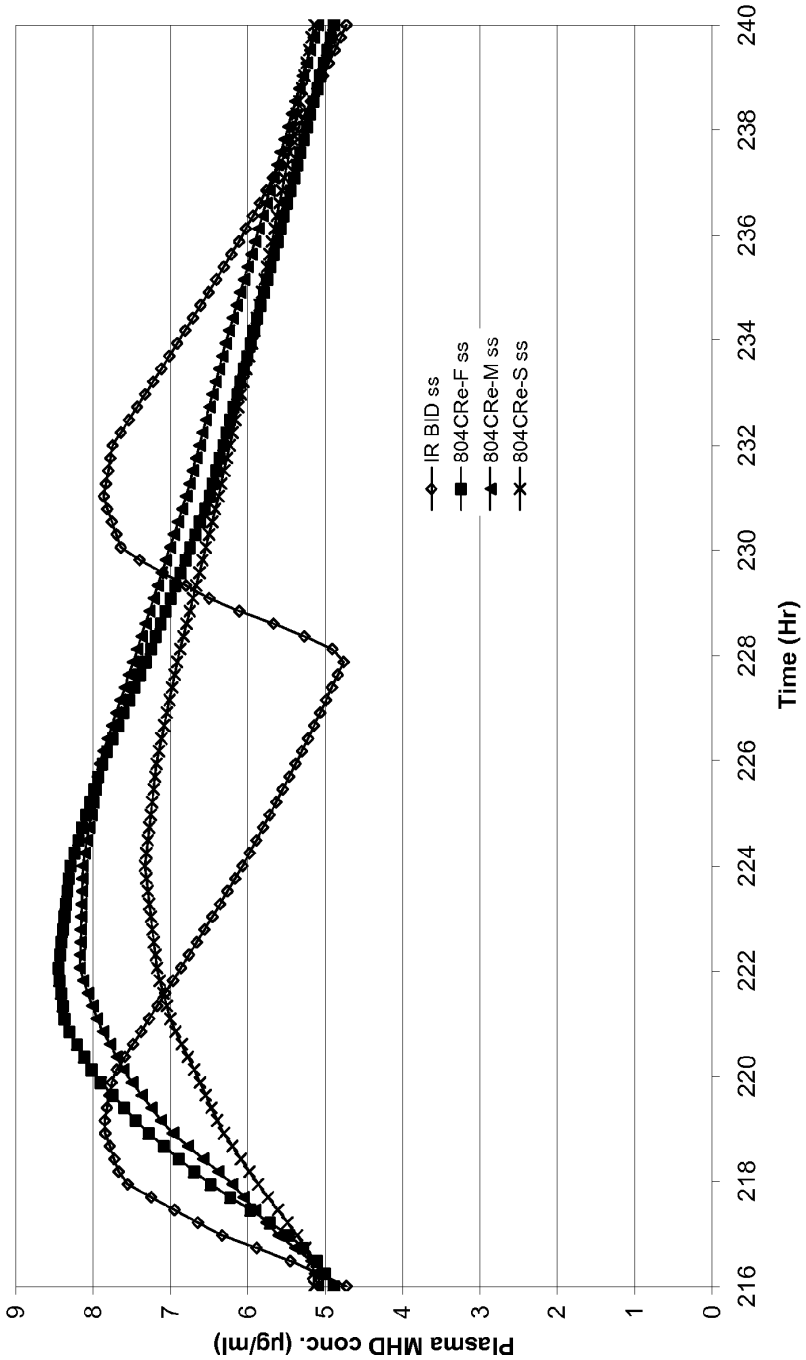

CRe-F, Lot B06016A
CRe-M, Lot B06017A
CRe-S, Lot B06018A
Trileptal 300mg
Plasma OXC conc. (µg/ml)
Time (Hr)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0
6
12
18
24
30
36
42
48
54
60
66
72

FIGURE 14


Plasma MHD conc. (µg/ml)
0
1
2
3
4
5
6
7
8
9
216
218
220
222
224
226
228
230
232
234
236
238
240
Time (Hr)
IR BID ss
804CRe-F ss
804CRe-M ss
804CRe-S ss

MODIFIED-RELEASE PREPARATIONS CONTAINING OXCARBAZEPINE AND DERIVATIVES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/794,837, filed Apr. 26, 2006, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention is directed to controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration.

BACKGROUND OF THE INVENTION

Oxcarbazepine belongs to the benzodiazepine class of drugs and is registered worldwide as an antiepileptic drug. Oxcarbazepine is approved as an adjunct or monotherapy for the treatment of partial seizures and generalized tonic-clonic seizures in adults and children. An immediate-release (IR) formulation of oxcarbazepine is currently on the market under the trade name Trileptal® and is administered twice a day to control epileptic seizures. Such immediate release compositions provide the drug to the patient in a manner that result in a rapid rise of the plasma drug concentration followed by a rapid decline. This sharp rise in drug concentration can result in side effects, and make multiple daily administration of the drug necessary in order to maintain a therapeutic level of the drug in the body. The need for a controlled-release dosage form for drugs taken chronically such as oxcarbazepine and derivatives is self-evident. Patient compliance is greatly improved with controlled-release (CR) dosage forms that are taken, for example, once-a-day. Also, there are significant clinical advantages such as better therapeutic efficacy as well as reduced side effects with controlled-release dosage forms.

Oxcarbazepine and its derivatives contemplated in this invention are poorly soluble in water. Due to their poor solubility, their release from a sustained release dosage form is rather incomplete. Whereas the in vitro release of oxcarbazepine is dependent on the dissolution method, including the dissolution media used, it has been found through in silico modeling that the release of oxcarbazepine in vivo from a traditional sustained-release dosage form is relatively low. This results in reduced bioavailability of the drug making the dosage form ineffective in providing a therapeutically effective concentration in the body. This poses a serious challenge to the successful development of sustained-release dosage forms for oxcarbazepine and its derivatives.

The rate of drug release from a dosage form has a significant impact on the therapeutic usefulness of the drug and its side effects. Hence, drug release profiles must be customized to meet the therapeutic needs of the patient. An example of a customized release profile is one that exhibits a sigmoidal release pattern, characterized by an initial slow release followed by fast release which is then followed by slow release until all of the drug has been released from the dosage form.

Sustained-release dosage forms for oxcarbazepine and derivatives have been described in the art. For example, Katzhendler et al. (U.S. Pat. No. 6,296,873) describes sustained-release delivery systems for carbamazepine and its derivatives. Katzhendler et al. teaches that a zero-order release profile is achieved for carbamazepine and derivatives through the use of hydrophilic and hydrophobic polymers. Zero-order (constant) release was achieved using high molecular weight hydroxypropyl methyl cellulose (HPMC) along with some optional hydrophobic excipients. A similar approach is taught by Shah et al. (US Patent Application 20020169145). Franke et al. (US Patent Application 20040142033) discloses sustained-release formulations of oxcarbazepine that are characterized by the release of 55%-85% of the drug in 15 minutes, and up to 95% in 30 minutes. According to the authors, such release profiles provide adequate sustained-release to achieve once-a-day administration of oxcarbazepine. However, the solubility and bioavailability of the drug from these enhanced preparations suitable for once-a-day administration. The prior art does not teach how to make preparations of oxcarbazepine and derivatives characterized by sigmoidal release profiles.

SUMMARY OF THE INVENTION

It is an object of this invention to provide controlled-release formulations of oxcarbazepine for once-a-day administration. The composition of this invention is administered once-a-day and yet meets the therapeutic need of the patient. It is another object of this invention to improve the bioavailability of oxcarbazepine and derivatives thereof. It is yet another object of this invention to meet the therapeutic need of the patient without causing "spikes" in blood drug concentration that may lead to toxicity. It is yet another object of this invention to keep the blood concentration of the drug within the therapeutic window. It is yet another object of this invention to minimize the fluctuation between the C_{max} and C_{min} that is typical of many immediate-release and sustained-release preparations.

Many, if not all, of these objectives may be achieved in this invention through formulations that comprise both solubility-enhancing agents and release-promoting agents, and are characterized by release profiles that meet the requirement for once-a-day administration. The objectives may also be achieved through the combination of a multiplicity of units with different release profiles in one dosage unit. Minipellets/granules/tablets, which can be mixed in a certain ratio, provide a dosage form that meets the above stated therapeutic objectives.

This invention also pertains to multi-layer tablets. Multi-layer tablets can be prepared with each layer releasing the drug at a rate that is different from the rate of release from another layer. In multi-layer tablets, each layer may or may not be coated.

All of the advantages that stem from once-daily administration of a drug apply to the compositions of this invention. Some of the specific advantages of this invention may be: reduced fluctuation between C_{max} and C_{min} during the course of treatment and hence better therapeutic profile, reduced side-effects, improved patient compliance, and improved bioavailability of the drug.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the dissolution profiles for the three exemplary (CR-F, CR-M, and CR-S) oxcarbazepine formulations containing no solubility/release enhancer. The profiles show a non-zero order release with a lag. The T_{80}s (time for 80% of the dose to be released in vitro) for the CR-F, CR-M, and CR-S formulations were 2 Hrs, 5 Hrs and 11 Hrs, respectively. USP Apparatus II at 60 RPM was used. Dissolution medium was 1% SLS in water.

FIG. **2** shows the human pharmacokinetic (PK) profiles with respect to oxcarbazepine for the three exemplary controlled-release formulations of example 1 versus an immediate-release reference product (Trileptal® 600 mg). The strength of each formulation is 600 mg oxcarbazepine per tablet.

FIG. **3** shows the PK profiles with respect to the metabolite of oxcarbazepine (MHD) for the three exemplary controlled-release formulations of example 1 versus an immediate-release reference product (Trileptal® 600 mg). The strength of each formulation is 600 mg oxcarbazepine per tablet.

FIG. **4** shows the solubility results of oxcarbazepine with selected excipients.

FIG. **5** shows the dissolution profiles of oxcarbazepine CR formulations with solubility enhancer (CRe), without solubility enhancer (CR) and a "fast formulation" (CR-F) developed in Example 1. The time to dissolve 80% of the drug (T_{80}) for CRe, CR, and CR-F are 5-6 Hrs, 8 Hrs, and 1.5 Hrs, respectively.

FIG. **6** shows the dissolution profiles for the fast (CRe-F), medium (CRe-M), and slow (CRe-S) oxcarbazepine formulations containing solubility/release enhancers. The T_{80}s for the CRe-F, CRe-M, and CRe-S are 1.5 Hrs, 5 Hrs, and 8 Hrs, respectively. USP Apparatus II at 60 RPM was used. Dissolution medium was 1% SLS in water.

FIG. **7** shows the canine pharmacokinetic profiles with respect to oxcarbazepine, comparing the enhanced formulation (CRe) with non-enhanced formulations containing oxcarbazepine (CR and CR-F).

FIG. **8** shows the canine pharmacokinetic profiles with respect to MHD, comparing the enhanced formulation (CRe) with non-enhanced formulations containing oxcarbazepine (CR and CR-F).

FIG. **9** shows the PK profiles shown in FIG. **8** with in silico predicted PK profile for a twice-a-day 300 mg IR.

FIG. **10** shows in silico predicted PK profiles for various in vitro release profiles.

FIG. **11** shows the in silico predicted in vivo release profiles for the systems in FIG. **10**.

FIG. **12** shows human plasma concentration vs. time profiles with respect to MHD of the three Oxcarbazepine CR formulations in Example 4 (CRe-F, CRe-M, CRe-S) and Trileptal® as an IR control, dosed BID.

FIG. **13** shows human plasma concentration vs. time profiles with respect to the oxcarbazepine of the three Oxcarbazepine CR formulations in Example 4 (CRe-F, CRe-M, CRe-S) and Trileptal® as an IR control, dosed BID.

FIG. **14** shows the in silico predicted steady-state plasma profiles for the three exemplary formulations (CRe-F, CRe-M, and CRe-S) described in Example 4.

DETAILED DESCRIPTION OF THE INVENTION

It is the object of this invention to provide controlled-release oxcarbazepine formulations suitable for once-a-day administration. It is an additional object of the invention to incorporate a combination of solubility-enhancing excipients and/or release-promoting agents into the formulations to enhance the bioavailability of oxcarbazepine and its derivatives. Such compositions are referred to as enhanced formulations.

Oxcarbazepine was formulated to provide release profiles characterized by slow release initially, followed by rapid release and then followed by another period of slow release. Such a release profile is known to those skilled in the art as sigmoidal. Oxcarbazepine formulations with sigmoidal release profiles were tested in human pharmacokinetic (PK) studies. Based on the human data, improvements were made to the formulations by incorporating solubility enhancers and/or release-promoting excipients (such formulation are referred to as enhanced formulations). The enhanced formulations were tested in canine models and were surprisingly found to provide significant increase in bioavailability of oxcarbazepine compared to formulations containing no solubility/release enhancing excipients.

The incorporation of solubility enhancing agents in formulations containing poorly soluble drugs such as oxcarbazepine has a profound effect on the in vivo solubility and hence bioavailability of the drugs. Enhancing the solubility of oxcarbazepine results in an increase in its bioavailability and hence in better therapeutic performance of the drug. A combination of solubility and release promoters is contemplated in this invention. Preferable release promoting agents are pH dependent polymers, also known as enteric polymers. These materials are well known to those skilled in the art and exhibit pH dependent solubility such that they dissolve at pH values higher than about 4.0, while remaining insoluble at pH values lower than 4.0. Solubilizers function by increasing the aqueous solubility of a poorly soluble drug. When a formulation containing both the enteric polymer and solubilizer is exposed to an aqueous media of pH higher than 4.0, the enteric polymer dissolves rapidly leaving a porous structure, resulting in increased contact surface between the aqueous medium and the poorly soluble drug. This increased surface area enhances the efficiency of the solubilizer(s), and hence, the overall solubility and release rate of the drug is enhanced to a point where it impacts the availability of the drug for systemic absorption in patients.

Excipients that function as solubility enhancers can be ionic and non-ionic surfactants, complexing agents, hydrophilic polymers, pH modifiers, such as acidifying agents and alkalinizing agents, as well as molecules that increase the solubility of poorly soluble drug through molecular entrapment. Several solubility enhancers can be utilized simultaneously. All enteric polymers that remain intact at pH value lower than about 4.0 and dissolve at pH values higher than 4.0, preferably higher than 5.0, most preferably about 6.0, are considered useful as release-promoting agents for this invention.

Suitable pH-sensitive enteric polymers include cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic monoester copolymer, methyl acrylate-methacrylic acid copolymer, methacrylate-methacrylic acid-octyl acrylate copolymer, etc. These may be used either alone or in combination, or together with the polymers other than those mentioned above. Preferred enteric polymers are the pharmaceutically acceptable methacrylic acid copolymers. These copolymers are anionic polymers based on methacrylic acid and methyl methacrylate and, preferably, have a mean molecular weight of about 135000. A ratio of free carboxyl groups to methyl-esterified carboxyl groups in these copolymers may range, for example, from 1:1 to 1:3, e.g. around 1:1 or 1:2. Such polymers are sold under the trade name Eudragit™ such as the Eudragit L series e.g. Eudragit L 12.5™, Eudragit L 12.5P™, Eudragit L100™, Eudragit L 100-55™, Eudragit L-30D™, Eudragit L-30 D-55™, the Eudragit S™ series e.g. Eudragit S 12.5™, Eudragit S 12.5P™, Eudragit S100™. The release promoters are not limited to pH dependent polymers. Other hydrophilic molecules that dissolve rapidly and leach out of the dosage form quickly leaving a porous structure can be also be used for the same purpose.

The release-promoting agent can be incorporated in an amount from 10% to 90%, preferably from 20% to 80% and most preferably from 30% to 70% by weight of the dosage unit. The agent can be incorporated into the formulation either prior to or after granulation. The release-promoting agent can be added into the formulation either as a dry material, or it can be dispersed or dissolved in an appropriate solvent, and dispersed during granulation.

Solubilizers preferred in this invention include surface active agents such as sodium docusate, sodium lauryl sulfate, sodium stearyl fumarate, Tweens® and Spans (PEO modified sorbitan monoesters and fatty acid sorbitan esters), poly(ethylene oxide)-polypropylene oxide-poly(ethylene oxide) block copolymers (aka Pluronics™); complexing agents such as low molecular weight polyvinyl pyrrolidone and low molecular weight hydroxypropyl methyl cellulose; molecules that aid solubility by molecular entrapment such as cyclodextrins, and pH modifying agents, including acidifying agents such as citric acid, fumaric acid, tartaric acid, and hydrochloric acid; and alkalizing agents such as meglumine and sodium hydroxide.

Solubilizing agents typically constitute from 1% to 80% by weight, preferably from 1% to 60%, more preferably from 1% to 50%, of the dosage form and can be incorporated in a variety of ways. They can be incorporated in the formulation prior to granulation in dry or wet form. They can also be added to the formulation after the rest of the materials are granulated or otherwise processed. During granulation, solubilizers can be sprayed as solutions with or without a binder.

This invention also contemplates controlled-release formulations comprising oxcarbazepine that release the drug at variable rates in the GI tract. It is also an object of this invention to design a drug delivery system to deliver drug at a very low rate early, followed by a relatively increased rate. It is another object of this invention to provide a drug release profile that is characterized by an immediate-release followed by a modified-release, such as extended-release (XR) or delayed-release (DR). These types of release profiles ensure that the C_{max} (maximum concentration of the drug in blood/plasma) is kept within the therapeutic window while extending the maintenance of an effective drug level in the body. The goal of this invention is to develop a controlled-release pharmaceutical composition of oxcarbazepine that provides steady-state blood levels of MHD, an active metabolite of oxcarbazepine, at a concentration of about 2 μg/ml to about 10 μg/ml. In the preferred embodiment, steady-state blood C_{max} levels of MHD fall in the range of about 6 μg/ml to about 10 μg/ml, and C_{min} levels of MHD fall in the range of about 2 μg/ml to about 5 μg/ml. Reduced fluctuation between C_{max} and C_{min} during the course of treatment results in a better therapeutic profile, reduced side-effects, improved patient compliance, and improved bioavailability of the drug.

The desired drug release pattern contemplated by this invention is achieved by using "matrix" polymers that hydrate and swell in aqueous media, such as biological fluids. As these polymers swell, they form a homogenous matrix structure that maintains its shape during drug release and serves as a carrier for the drug, solubility enhancers and/or release promoters. The initial matrix polymer hydration phase results in slow-release of the drug (lag phase). Once the polymer is fully hydrated and swollen, the porosity of the matrix increases due to the leaching out of the pH-dependent release promoters, and drug is released at a faster rate. The rate of the drug release then becomes constant, and is a function of drug diffusion through the hydrated polymer gel.

Thus, the release vs. time curve is characterized by at least two slopes: one slope for the lag phase where drug release rate is low and a second slope where drug release is faster. The slope of the rising part of the release vs. time curve can be customized as to match the rate at which the drug is eliminated from the body. A desired release profile can be achieved by using swellable polymers alone or in combination with binders, such as gelling and/or network forming polymers.

The water-swellable, matrix forming polymers useful in the present invention are selected from a group comprising cellulosic polymers, such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), methylcellulose (MC), powdered cellulose such as microcrystalline cellulose, cellulose acetate, sodium carboxymethylcellulose, calcium salt of carboxymethylcellulose, and ethylcellulose; alginates, gums such as guar and xanthan gums; cross-linked polyacrylic acid derivatives such as Carbomers (aka Carbopol™) available in various molecular weight grades from Noveon Inc. (Cinncinatti, Ohio); carageenan; polyvinyl pyrrolidone and its derivatives such as crospovidone; polyethylene oxides; and polyvinyl alcohol. Preferred swellable polymers are the cellulosic compounds, HPMC being the most preferred.

The swellable polymer can be incorporated in the formulation in proportion from 1% to 50% by weight, preferably from 5% to 40% by weight, most preferably from 5% to 20% by weight. The swellable polymers and binders may be incorporated in the formulation either prior to or after granulation. The polymers can also be dispersed in organic solvents or hydro-alcohols and sprayed during granulation.

It is yet another aspect of this invention to prepare formulations of oxcarbazepine that combine multiple modified-release "units," each "unit" prepared according to any one or more of the above-disclosed dosage forms, to provide for a customized release profile.

The modified-release units comprise minipellets/granules/tablets etc., each with unique release profiles, that can be mixed in a certain ratio to provide a dosage form that meets the above-stated therapeutic objectives. Alternatively, multiple modified release units may be formed into of multi-layer tablets. Multi-layer tablets can be prepared with each layer releasing the active compound at a rate that is different from the rate of release of the active ingredient from another layer. In multi-layer tablets, each layer may optionally be coated with controlled-release polymer(s). The combination dosage forms can exhibit release profiles that comprise any/all possible combinations of immediate release (IR), delayed release (DR), and extended release (XR) formulations. Pellets/granules/tablets or each layer of a single tablet may optionally be coated.

Various hydrophobic excipients can be used to modify the hydration rate of the dosage unit when exposed to water or aqueous media. These excipients retard the wetting of the dosage unit and hence modify the release of the active agent. Hydrophobic excipients suitable for this invention are represented by, but not limited to, glyceryl monstearate, mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex, Eastman Fine Chemical Company), glycerylmonooleate, a mixture of mono, di and tri-glycerides (ATMUL 84S), glycerylmonolaurate, glyceryl behenate, paraffin, white wax, long chain carboxylic acids, long chain carboxylic acid esters and long chain carboxylic acid alcohols.

Examples of saturated straight chain acids, useful with the invention, are n-dodecanoic acid, n-tetradecanoic acid, n-hexadecanoic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid and melissic acid. Also useful are unsaturated monoolefinic straight chain monocarboxylic acids. Examples of these are oleic acid, gadoleic acid

and erucic acid. Also useful are unsaturated (polyolefinic) straight chain monocarboxylic acids such as linoleic acid, linolenic acid, arachidonic acid and behenolic acid. Useful branched acids include, for example, diacetyl tartaric acid.

Examples of long chain carboxylic acid esters include, but are not limited to: glyceryl monostearates; glyceryl monopalmitates; mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex 600, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monooleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate and glyceryl monolinoleate (Myverol 18-92, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monogadoleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate, glyceryl monolinoleate, glyceryl monolinoleate and glyceryl monogadoleate (Myverol 18-99, Eastman Fine Chemical Company); acetylated glycerides such as distilled acetylated monoglycerides (Myvacet 5-07, 7-07 and 9-45, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company), d-alpha tocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS, Eastman Chemical Company); mixtures of mono- and diglyceride esters such as Atmul (Humko Chemical Division of Witco Chemical); calcium stearoyl lactylate; ethoxylated mono- and di-glycerides; lactated mono- and di-glycerides; lactylate carboxylic acid ester of glycerol and propylene glycol; lactylic esters of long chain carboxylic acids; polyglycerol esters of long chain carboxylic acids, propylene glycol mono- and di-esters of long chain carboxylic acids; sodium stearoyl lactylate; sorbitan monostearate; sorbitan monooleate; other sorbitan esters of long chain carboxylic acids; succinylated monoglycerides; stearyl monoglyceryl citrate; stearyl heptanoate; cetyl esters of waxes; cetearyl octanoate; C_{10}-C_{-30} cholesterol/lavosterol esters; and sucrose long chain carboxylic acid esters. In addition, waxes can be useful alone or preferably in combination with the materials listed above. Examples of these are white wax, paraffin and carnauba wax.

Drug, polymers, and other excipients are typically combined and wet granulated using a granulating fluid. However, other methods of forming granules such as slugging, and roller compaction can also be used to manufacture matrix granules. Matrix tablets can also be made by direct compression. In wet granulation, typical granulating fluids are: water, a mixture of water and alcohol, anhydrous alcohol. Wet granules can be made in any granulating device such as mixers, high shear granulators, and fluid bed granulators. Granules can be dried in appropriate drying equipment such as fluid bed dryers, ovens, microwave dryers etc. Granules can also be air-dried. Dried granules can be milled using appropriate milling device to achieve a particular particle size distribution. Granules can be filled in to capsules, or blended with other excipients and tableted on a tablet press. Granules can also be packaged into sachets for sprinkle application. Other excipients used to aid tableting are well known to those skilled in the art and include magnesium stearate, talc, cabosil etc. Granules and tablets can, optionally, be coated to further modify release rates. Furthermore, formulations can also optionally contain dyes.

Optionally, but preferably, the tablet composition can contain one or more lubricants, which may be added to assure proper tableting. Non-limiting examples of lubricants include magnesium stearate, calcium stearate, zinc stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, sodium stearyl fumarate, hydrogenated vegetable oils, and other waxes, including but not limited to, beeswax, carnuba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, and stearyl alcohol. The lubricant, when present, is typically included in an amount of from about 0.1 wt. % to about 20 wt. % of the composition, preferably from about 1 to about 10 wt. %, and more preferably about 0.3 to about 3.0 wt. %.

The oxcarbazepine dosage can be formulated into tablets, granules, and pellets. The steps involved in the manufacturing of these dosage forms are well known to those skilled in the art. Briefly, tablets can be compressed from directly compressible blend containing the active or pre-formed granules. The tablets can be coated or not coated. The coating may optionally impart modification of release. Granules can be made by high shear granulation or fluid bed processing. The granules may or may not be coated. Pellets can be manufactured by drug layering on inert carriers such as sugar spheres. Pellets can also be manufactured by extrusion/spheronization process. The pellets may or may not be coated. Coated pellets and granules can be filled into capsules.

Formulations of this invention can also be made in pelletized forms, which can be filled into capsules or dispensed in sachets for sprinkle application. Each pellet is composed of the drug, swellable polymer(s) and other excipients that aid the processing. Pellets can be prepared in one of the many ways that are known by those skilled in the art. These include, for example, extrusion/spheronization and roller compaction (slugging). In the extrusion/spheronization technique, drug is mixed with swellable polymer(s), such as cellulosic polymers and other excipients. The blend is then granulated in a high shear granulator. The wet mass is then passed through an extruder and spheronized using a spheronizer. The pellets are then dried in an oven or fluid bed processor. The dried pellets are either processed further or encapsulated without further processing.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The invention now will be described in particularity with the following illustrative examples; however, the scope of the present invention is not intended to be, and shall not be, limited to the exemplified embodiments below.

EXAMPLES

Example 1

Oxcarbazepine Formulations with Sigmoidal Release Profiles

Table 1 provides the formula composition of oxcarbazepine controlled-release preparations with sigmoidal release profiles. Granules were prepared by high shear granulation using anhydrous ethanol as the granulating liquid. All ingredients, except for magnesium stearate, were charged in to VG-65/10 M high shear granulator. The dry powders are blended by running the blade for 3 minutes, after which time the anhydrous ethanol was sprayed onto the mixing blend at a spray rate of approximately 40-60 gm/min. After about a minute of spray, the chopper on the VG-65/10 M was started

and run throughout the spray. Once the granulation was completed, the granulation was discharged from the VG high shear granulator, spread on an appropriate tray and placed in an oven to dry at 40° C. for 24 Hrs. Alternatively, granules can be dried using a fluid bed processor. Dry granules were screened through an 18-mesh screen. Screened granules were blended with magnesium stearate in a proportion of 99.5% granules and 0.5% magnesium stearate. The blend was then tableted on a rotary tablet press.

TABLE 1

Formula composition of Oxcarbazepine CR formulations with changing slope

Ingredients	SLI 530 CR-F (Fast)	SLI530 CR-M (Medium)	SLI530 CR-S (Slow)
Oxcarbazepine	60	60	60
Compritol 888ATO	9.5	7	—
Prosolv HD90	9.8	20.3	15
Kollidon 25	10	—	—
Kollidon 90	—	3	—
Methocel E5 Prem. LV	—	—	10
Methocel K4M Premium CR	—	—	5
Carbopol 971P	10	9	9
Mg Stearate	0.5	0.5	0.5
FD&C Red #40	—	—	0.5
FD&C Blue #1	0.2	—	—
FD&C Yellow #6	—	0.2	—
Anhydrous Ethanol	*	*	*
Total	100	100	100

*Removed during processing

FIG. **1** shows the dissolution profiles of three exemplary oxcarbazepine CR formulations (CR-F, CR-M, and CR-S). The profiles exhibited non-zero order release.

Example 2

Human Pharmacokinetic Evaluation of Oxcarbazepine CR Formulations from Example 1

The three formulations from the Example 1 were evaluated in humans to obtain pharmacokinetic information. An immediate release tablet (Trileptal® 600 mg) was used as a control reference. The formulations were examined in a randomized, single dose, crossover study in healthy human volunteers. Blood samples were analyzed for both the parent molecule oxcarbazepine and its metabolite (the monohydroxy derivative, MHD).

Table 2 provides the mean PK parameters for MHD. The PK profiles are shown in FIGS. **2** and **3**.

TABLE 2

Pharmacokinetic parameters of the three exemplary formulations in example 1 and immediate release reference product.

PK Parameters	CR-F Fast	CR-M Med	CR-S Slow	Trileptal ™ IR
T_{max} (Hr)	6.5	8.4	9.1	1.4
C_{max} (ug/mL)	0.248	0.146	0.103	1.412
AUC_{last} (Hr * ug/mL)	3.0	2.5	1.7	5.7
Rel BA	53%	44%	30%	100%

Example 3

Solubility Enhancers Screening

The solubility of oxcarbazepine in the presence of excipients was evaluated as follows:

Excipients were dissolved in phosphate buffer to make solutions with concentrations shown in Table 3. One gram of oxcarbazepine was then mixed with 19 μm of the excipient solution. The mixture was rocked overnight at room temperature and then filtered using 0.22 μm filter. The filtrates were analyzed by HPLC. The solubility results are given in Table 3 and FIG. **4**.

TABLE 3

Solubility of Oxcarbazepine in the presence of excipients

Excipients	Excipient conc. (% w/w)	Solubility (mg/mL)
Phosphate Buffer Control	NA	0.4009
Hydroxypropyl betacyclodextrin (HBCD)	5	1.0218
Sodium Lauryl Sulfate (SLS)	5	4.1113
Kollidon 17	1	0.1717
SLS/HBCD	1, 1	0.3489
Cremophor RH40	1	0.3140
Docusate Sodium	5	6.5524
SLS/Polyethylene Glycol 400 (PEG400)	5, 1	3.0516
SLS/Stearic Acid/PEG400	5, 1, 1	3.2821
De-ionized Water	NA	0.2733

Example 4

Formulation of Enhanced Dosage Forms

Tables 4 and 5 provide the composition of the formulation containing solubility- and release-enhancing agents. Granules were manufactured by high shear granulation using water as the granulating liquid. All ingredients, except for magnesium stearate, were charged into a VG-65/10 M high shear granulator. The dry powders were blended by running the blade for 3 minutes, upon which time water was sprayed onto the mixing blend at a spray rate of approximately 40-60 gm/min. After about a minute of spray, the chopper on the VG-65/10 M was started and run throughout the spray. Once the granulation was completed, the granulation was discharged from the VG high shear granulator, spread on an appropriate tray and placed in an oven to dry at 40° C. for 24 Hrs. Alternatively, granules can be dried using a fluid bed processor. Dry granules are screened through an 18-mesh screen. Screened granules were blended with magnesium stearate in a proportion of 99.5% granules and 0.5% magnesium stearate. The resulting blend was then tableted on a rotary tablet press. Dissolution profiles for these formulations are shown in FIGS. **5** and **6**.

TABLE 4

Percent Composition of Enhanced (CRe-M) and non-Enhanced (CR) Prototypes

Formulation	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
Oxcarbazepine	60	60
Prosolv SMCC50	10	25
PVP K25	5	5

TABLE 4-continued

Percent Composition of Enhanced (CRe-M) and non-Enhanced (CR) Prototypes

Formulation	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
HPMC K4M premium	10	10
SLS	5	0
Eudragit L100-55	10	0
Magnesium Stearate	0.5	0.5

TABLE 5

Percent Composition for the three exemplary enhanced formulations: CRe-F, CRe-M, and CRe-S.

Formulation	% PD0294-046 CRe-F	% PD0294-051 CRe-M	% PD0294-054 CRe-S
Oxcarbazepine	60	60	60
Prosolv SMCC50	15	10	5
PVP K25	5	5	5
HPMC K4M premium	5	10	15
SLS	5	5	5
Eudragit L100-55	10	10	10
Magnesium Stearate	0.5	0.5	0.5

Example 5

Canine PK Studies on Formulations from Example 4. Table 4 and Example 1. (SLI530CR-F)

Six male beagle dogs were dosed orally with the formulations in the order given in Table 6. Blood was drawn over a 24 Hr period and blood samples were analyzed by HPLC. A noncompartmental analysis of the data was used to generate T_{max}, C_{max}, AUC_{last}, and AUC_{inf}. Relative Bioavailability was calculated in Excel using the AUC_{last} and AUC_{inf} for the CRf formulation as the control. The PK profiles for oxcarbazepine and 10-hydroxycarbazepine are given in FIGS. **7** and **8**.

TABLE 6

Prototypes tested in dogs

Phase	Test Article	SLI Lot #	Dose (mg)
1	Oxcarbazepine CR	PD0294-024A	600
2	Oxcarbazepine CRe	PD0294-024B	600
3	Oxcarbazepine CR-F	B04032	600

TABLE 7

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine

Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CRe-M) PD0294-024B	Fast CR (CR-F) B04032
T_{max}	1.5	1.8	1.7
C_{max}	1.20	1.72	0.7

TABLE 7-continued

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine

Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CRe-M) PD0294-024B	Fast CR (CR-F) B04032
AUC_{last}	3.44	7.98	3.41
AUC_{inf}	3.74	11.09	4.01
Rel BA_{last}	101%	234%	100%
Rel BA_{inf}	93%	276%	100%

Example 6

In Silico Modeling of Various Release Profiles of Oxcarbazepine XR

In silico modeling was carried out for various hypothetical systems. Results are shown in FIGS. **9-11**.

Example 7

Human Pharmacokinetic Evaluation of Solubility Enhanced Oxcarbazepine CR Formulations from Example 4

The three solubility enhanced prototypes from the Example 4 were evaluated in humans to obtain pharmacokinetic information. An immediate release tablet (Trileptal® 300 mg) given BID was used as a reference. The formulations were examined in a randomized, single dose, crossover study in healthy human volunteers. Blood samples were analyzed for both the parent molecule oxcarbazepine and its metabolite (the monohydroxy derivative, MHD).

Table 8 provides the mean PK parameters for MHD. The PK profiles are shown in FIGS. **12** and **13**.

TABLE 8

Pharmacokinetic parameters of the three exemplary solubility enhanced formulations in Example 4 and Trileptal ™

PK Parameters	CRe-F Fast	CRe-M Med	CRe-S Slow	Trileptal ™ BID
T_{max} (Hr)	9	11	14	16
C_{max} (ug/mL)	5.32	5.14	4.40	6.23
AUC_{last} (Hr * ug/mL)	160.3	161.3	148.9	167.1
Rel BA	96%	97%	89%	100%

What is claimed is:

1. A pharmaceutical formulation for once-a-day administration of oxcarbazepine comprising a homogeneous matrix comprising:

(a) oxcarbazepine;

(b) a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;

(c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and

(d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhy-

droxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, and Eudragit L100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers.

2. The formulation of claim **1**, wherein the surface active agents comprise sodium docusate, sodium lauryl sulfate, sodium stearyl fumarate, polyethylene oxide (PEO) modified sorbitan monoesters, fatty acid sorbitan esters, polyethylene oxide-polypropylene oxide-(poly(ethylene oxide)) block copolymers, or combinations thereof.

3. The formulation of claim **1**, wherein the cellulosic polymers are selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), methylcellulose (MC), powdered cellulose, cellulose acetate, sodium carboxymethylcellulose, calcium salt of carboxymethylcellulose, and ethylcellulose.

4. The pharmaceutical formulation of claim **1**, wherein the release promoting agent is incorporated in an amount from 10% to 90% by weight of the formulation, and the agent that enhances the solubility of oxcarbazepine is incorporated in an amount from 1% to 80% by weight of the formulation.

5. The pharmaceutical formulation of claim **4**, wherein the release promoting agent is incorporated in an amount from 30% to 70% by weight of the formulation, and the agent that enhances the solubility of oxcarbazepine is incorporated in an amount from 1% to 80% by weight of the formulation.

6. The pharmaceutical formulation of claim **1**, wherein the amount of oxcarbazepine is effective to produce a steady state blood level of monohydroxy derivative of oxcarbazepine in the range of about 2 μg/ml to about 10 μg/ml.

7. The pharmaceutical formulation of claim **1** wherein the formulation is effective in minimizing fluctuations between C_{min} and C_{max} of monohydroxy derivative of oxcarbazepine.

8. The pharmaceutical formulation of claim **7**, which provides C_{max} levels of monohydroxy derivative of oxcarbazepine in the range of about 6 μg/ml to about 10 μg/ml and C_{min} levels of monohydroxy derivative of oxcarbazepine in the range of about 2 μg/ml to about 5 μg/ml.

9. The formulation of claim **1**, wherein the amount of oxcarbazepine is 600 mg.

10. The pharmaceutical formulation of claim **1** in the form of pellets, tablets, granules or capsules.

11. The formulation of claim **10** in the form of tablets.

12. The formulation of claim **11**, wherein each tablet comprises 600 mg of oxcarbazepine.

13. The formulation of claim **1**, wherein the matrix-forming polymer is present in the amount of 1% to 50% by weight of the formulation.

14. The formulation of claim **1**, further comprising a lubricant selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, sodium stearyl fumarate, hydrogenated vegetable oils, and waxes.

15. The formulation of claim **1**, wherein the wax is selected from the group consisting of beeswax, camuba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, and stearyl alcohol.

16. The formulation of claim **12** wherein the lubricant is incorporated in an amount of from 0.1% to 20% by weight of the formulation.

17. The pharmaceutical formulation of claim **1**, wherein the polymer having pH-dependent solubility remains intact at pH values of below 4 and dissolves at pH values of more than 4.

18. The pharmaceutical formulation of claim **1**, wherein the polymer having pH-dependent solubility dissolves at pH values of more than 5.

19. The pharmaceutical formulation of claim **1**, wherein the polymer having pH-dependent solubility dissolves at pH values of more than 6.

20. The formulation of claim **1** comprising HPMC and polyvinyl pyrrolidone as matrix-forming polymers; sodium lauryl sulfate as the agent that enhances the solubility of oxcarbazepine, and Eudragit L100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)) as the release promoting agent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,722,898 B2
APPLICATION NO. : 11/734874
DATED : May 25, 2010
INVENTOR(S) : Padmanabh P. Bhatt et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Col. 14, line 16 “claim 1” should be --- claim 14

Col. 14, line 20 “claim 12” should be --- claim 14

Signed and Sealed this
Twenty-second Day of April, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

(12) **United States Patent**
Bhatt et al.

(10) **Patent No.: US 7,910,131 B2**
(45) **Date of Patent: *Mar. 22, 2011**

(54) **METHOD OF TREATING SEIZURES USING MODIFIED RELEASE FORMULATIONS OF OXCARBAZEPINE**

(75) Inventors: **Padmanabh P. Bhatt**, Rockville, MD (US); **Argaw Kidane**, Montgomery Village, MD (US); **Kevin Edwards**, Lovettsville, VA (US)

(73) Assignee: **Supernus Pharmaceuticals, Inc.**, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 170 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/230,276**

(22) Filed: **Aug. 27, 2008**

(65) **Prior Publication Data**

US 2009/0004263 A1 Jan. 1, 2009

Related U.S. Application Data

(63) Continuation of application No. 11/734,874, filed on Apr. 13, 2007, now Pat. No. 7,722,898.

(60) Provisional application No. 60/794,837, filed on Apr. 26, 2006.

(51) **Int. Cl.**
A61K 9/20 (2006.01)

(52) **U.S. Cl.** **424/464**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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http://www.merriam-westercom/dictionary/matrix (accessed Dec. 8, 2008), 3 pages.

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Primary Examiner — Michael G Hartley
Assistant Examiner — Paul Dickinson
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP; Stephen B. Maebius; Sunit Talapatra

(57) **ABSTRACT**

Controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration are disclosed. The inventive compositions comprise solubility- and/or release enhancing agents to provide tailored drug release profiles, preferably sigmoidal release profiles. Methods of treatment comprising the inventive compositions are also disclosed.

24 Claims, 14 Drawing Sheets

FIGURE 1

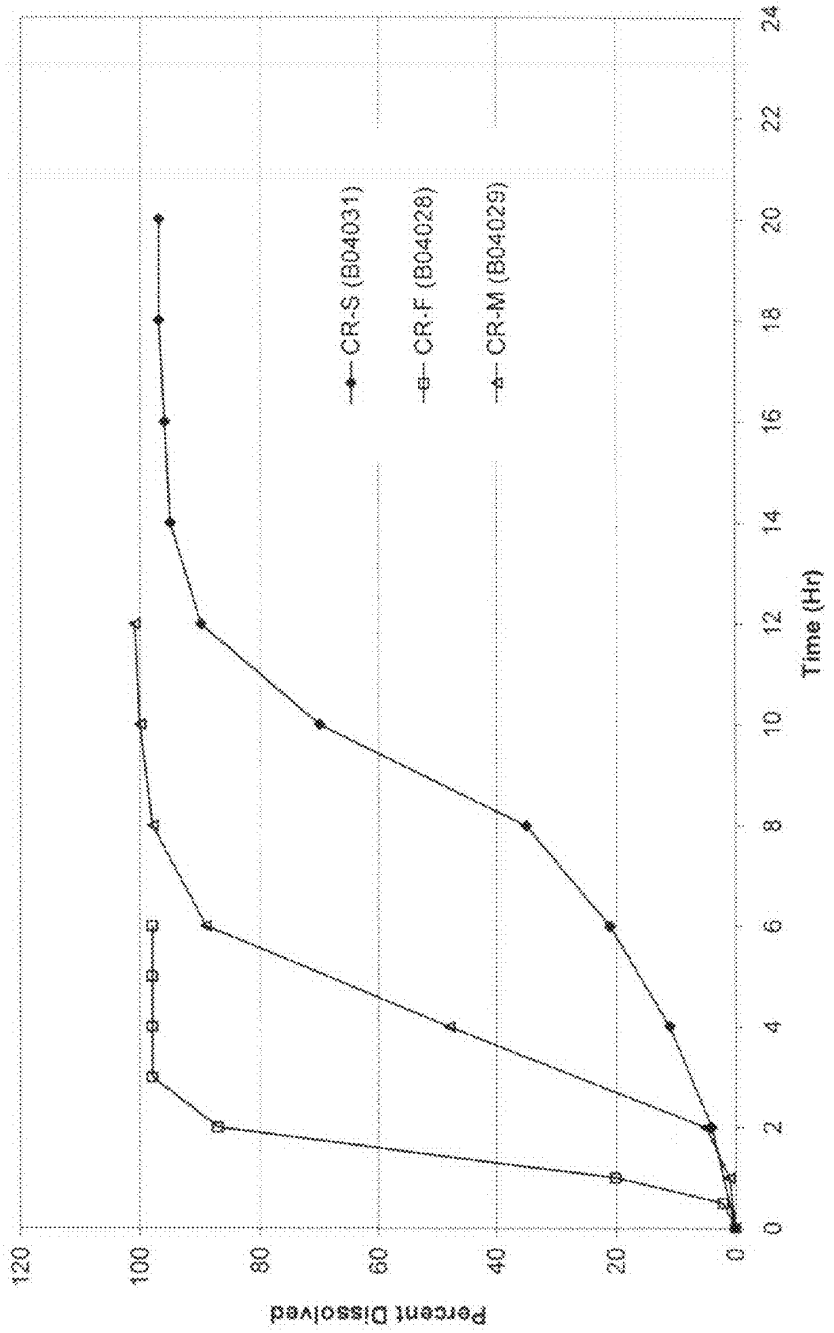

CR-S (B04031)
CR-F (B04028)
CR-M (B04029)
Percent Dissolved
Time (Hr)
0
20
40
60
80
100
120
0
2
4
6
8
10
12
14
16
18
20
22
24

FIGURE 2

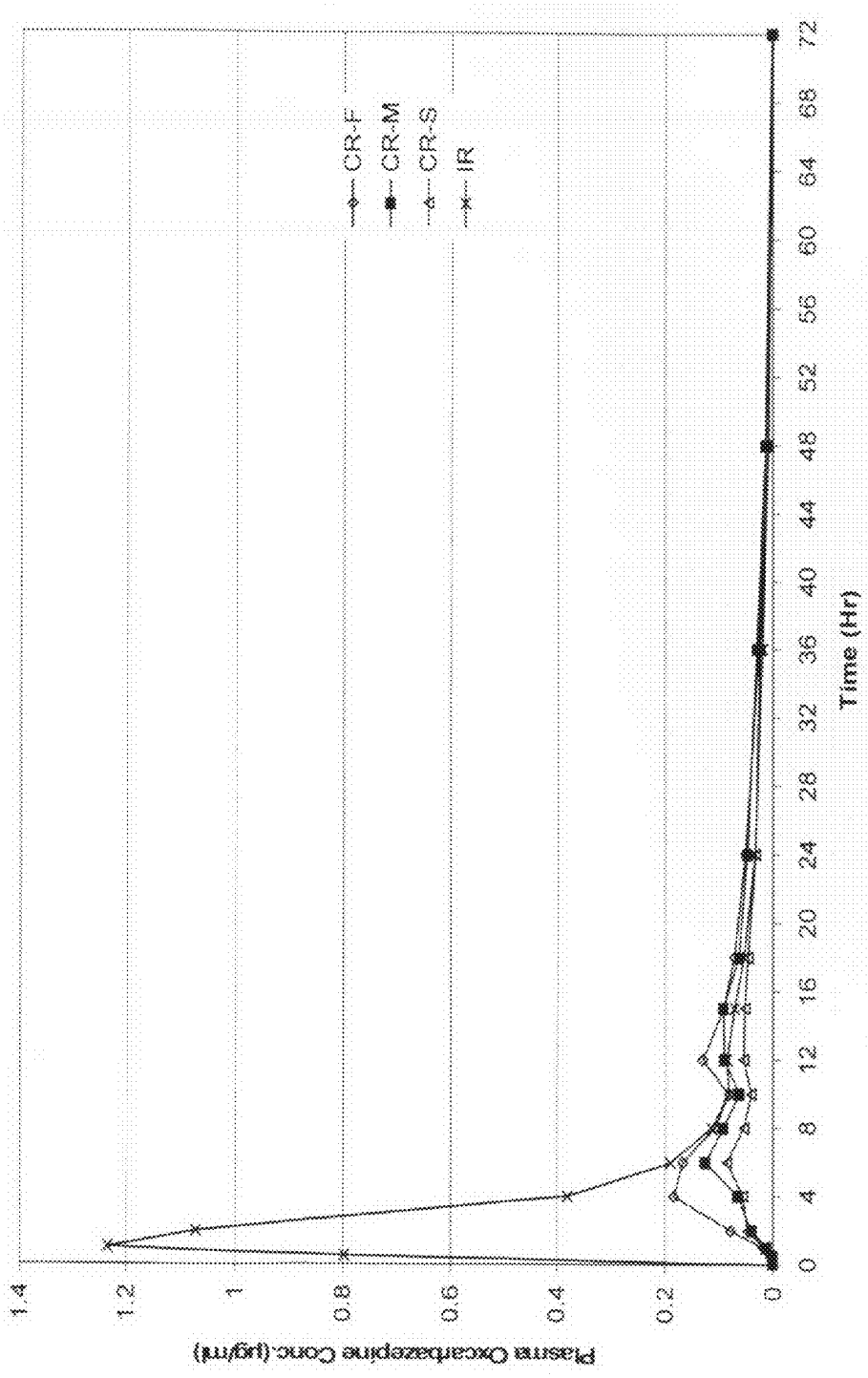

CR-F
CR-M
CR-S
IR
Plasma Oxcarbazepine Conc.(µg/ml)
Time (Hr)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72

FIGURE 3

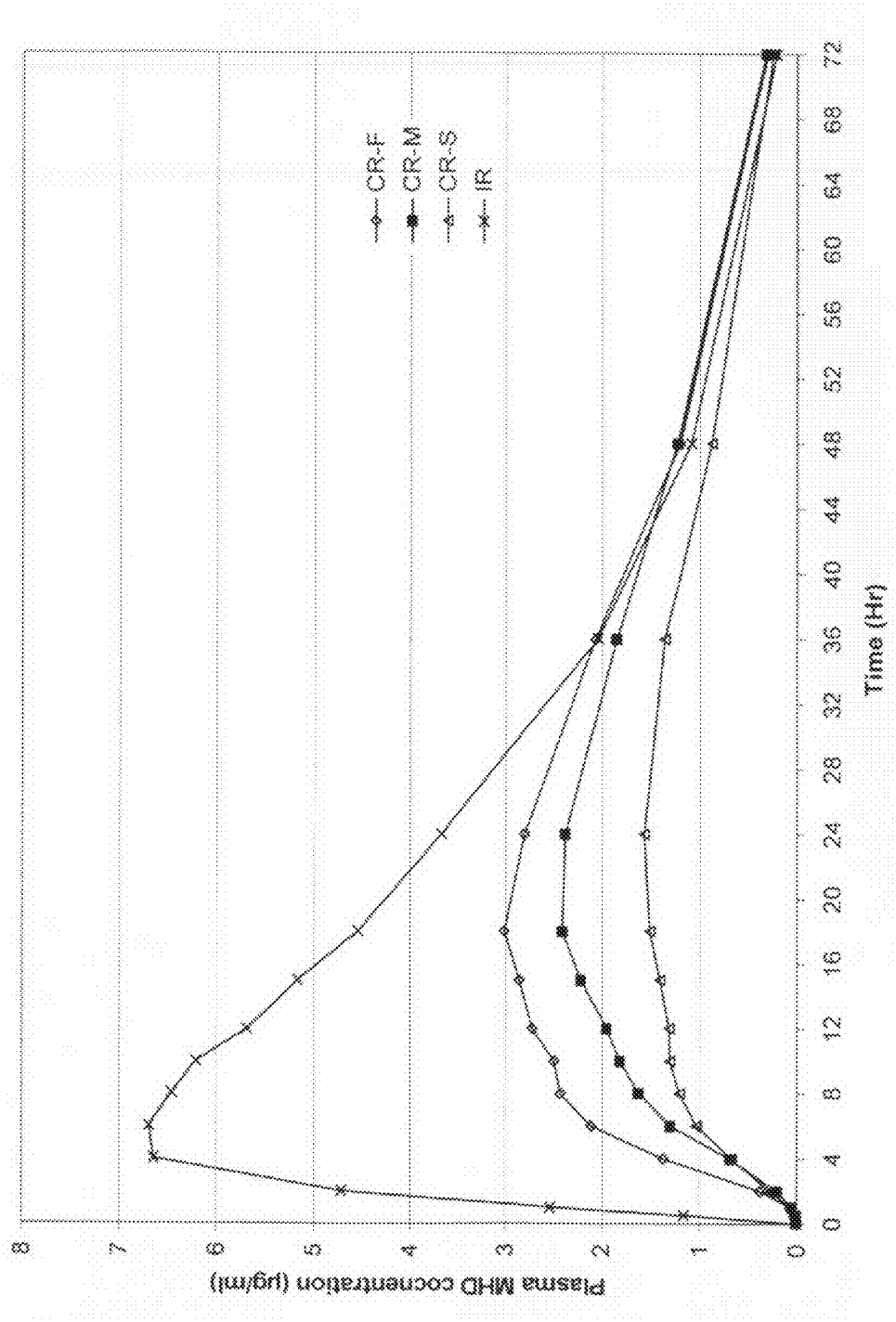

CR-F
CR-M
CR-S
IR
Plasma MHD concentration (µg/ml)
Time (Hr)
0
1
2
3
4
5
6
7
8
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
64
68
72

FIGURE 4

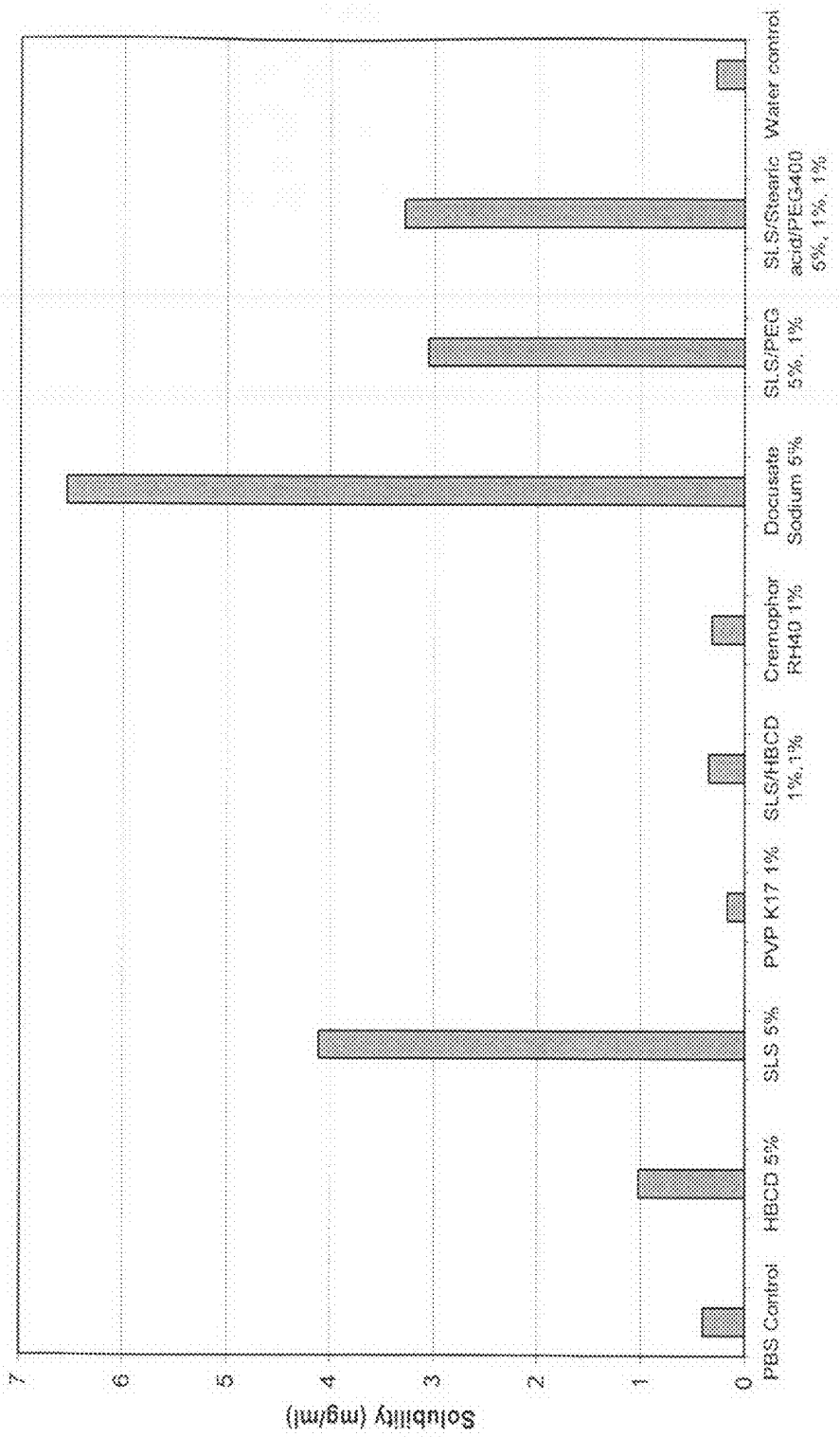

Solubility (mg/ml)
0
1
2
3
4
5
6
7
PBS Control
HBCD 5%
SLS 5%
PVP K17 1%
SLS/HBCD 1%, 1%
Cremophor RH40 1%
Docusate Sodium 5%
SLS/PEG 5%, 1%
SLS/Stearic acid/PEG400 5%, 1%, 1%
Water control

FIGURE 5

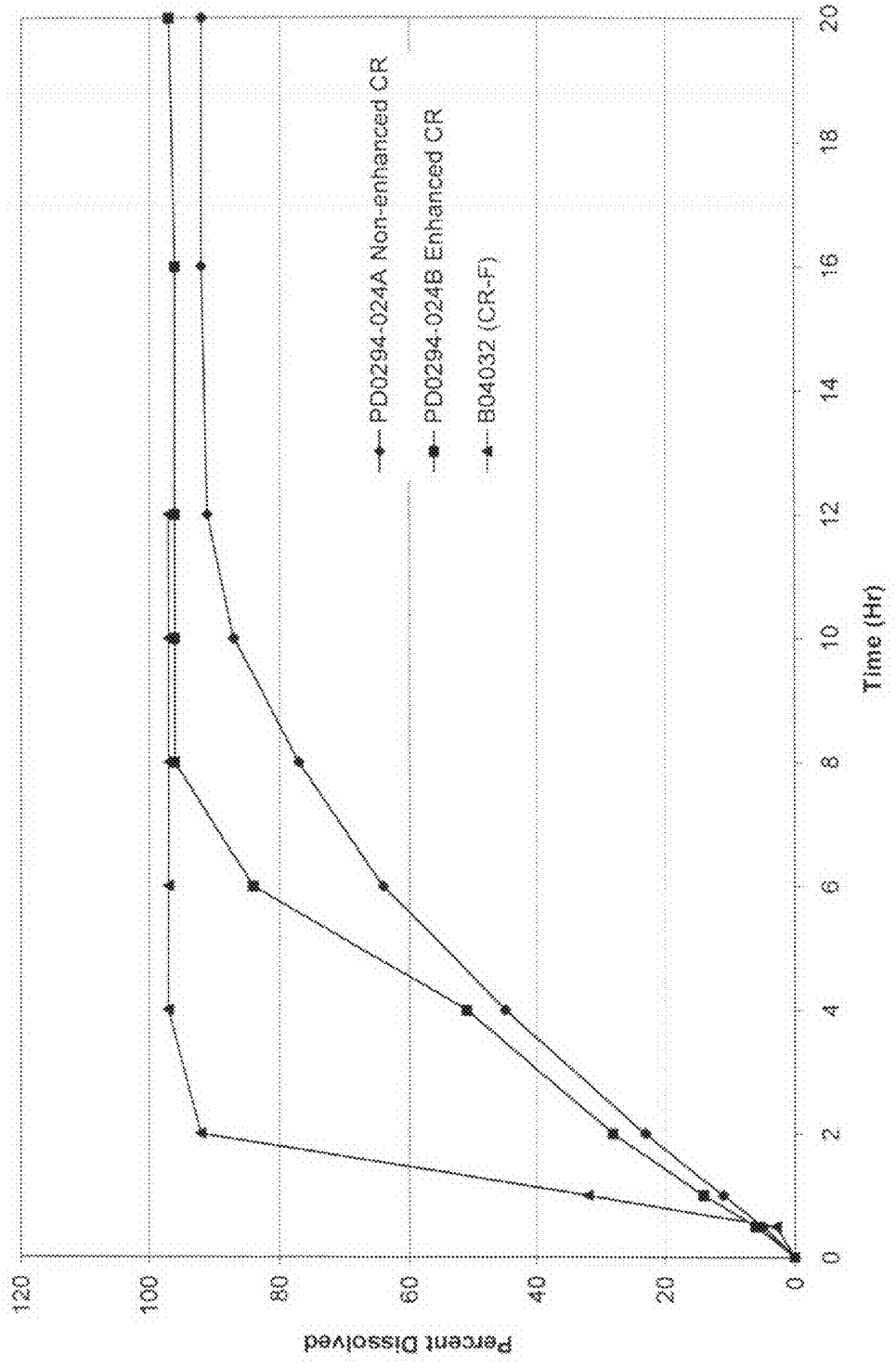

PD0294-024A Non-enhanced CR
PD0294-024B Enhanced CR
B04032 (CR-F)
Percent Dissolved
Time (Hr)
0
20
40
60
80
100
120
0
2
4
6
8
10
12
14
16
18
20

FIGURE 6

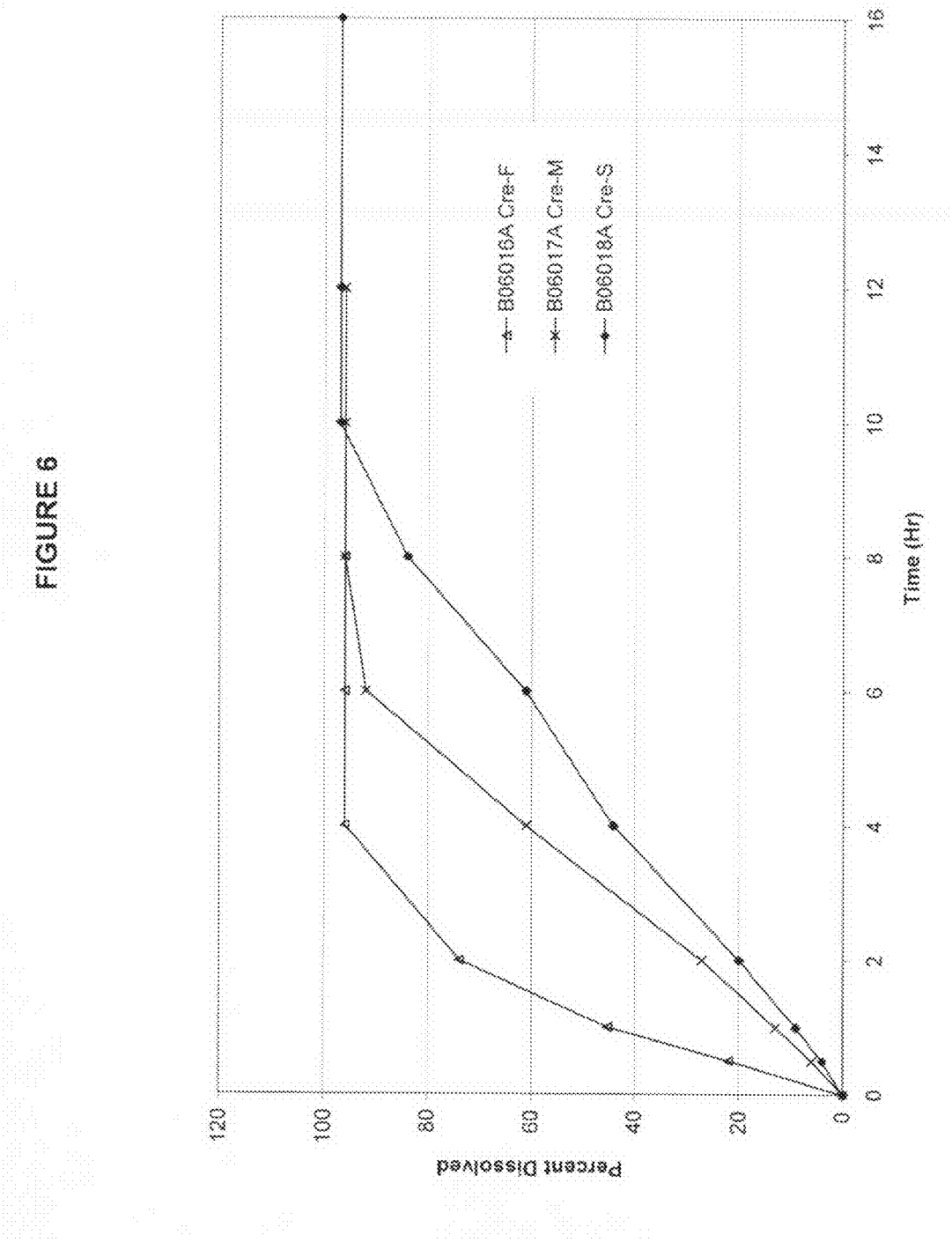

B06016A Cre-F
B06017A Cre-M
B06018A Cre-S
Percent Dissolved
0
20
40
60
80
100
120
Time (Hr)
0
2
4
6
8
10
12
14
16

FIGURE 7

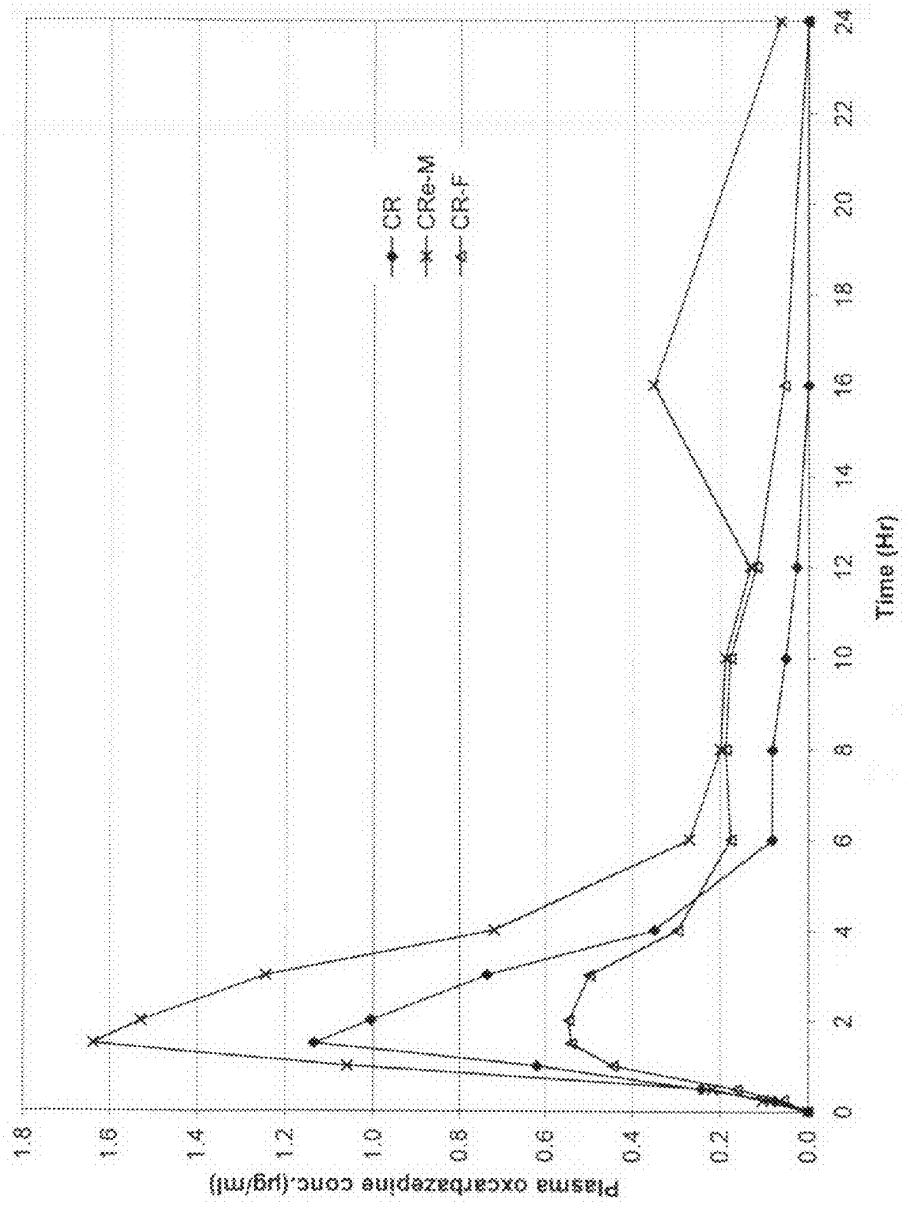

CR
CRe-M
CR-F
Plasma oxcarbazepine conc.(ug/ml)
Time (Hr)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
0
2
4
6
8
10
12
14
16
18
20
22
24

FIGURE 8

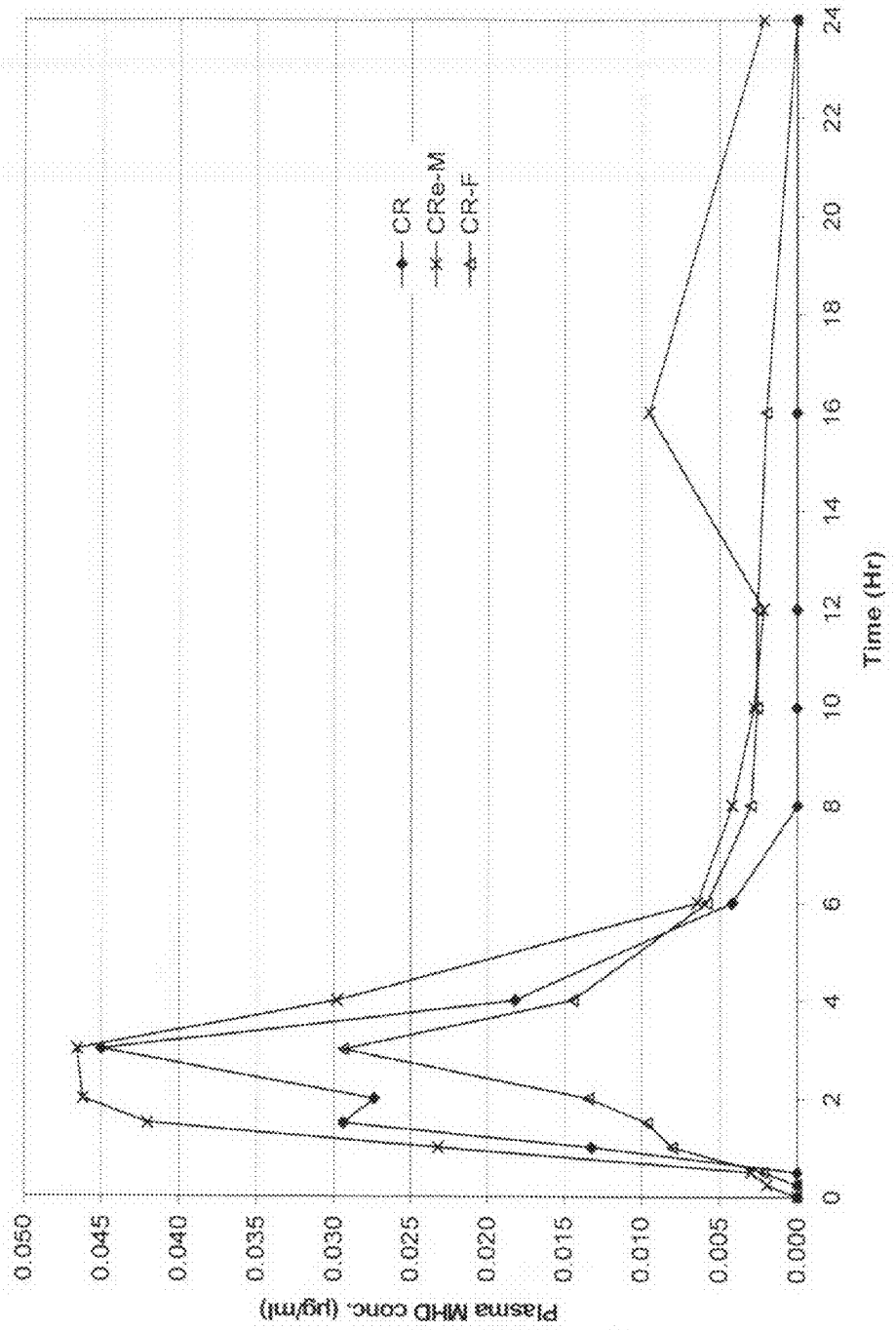

CR
CRe-M
CR-F
Plasma MHD conc. (µg/ml)
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
Time (Hr)
0
2
4
6
8
10
12
14
16
18
20
22
24

FIGURE 9

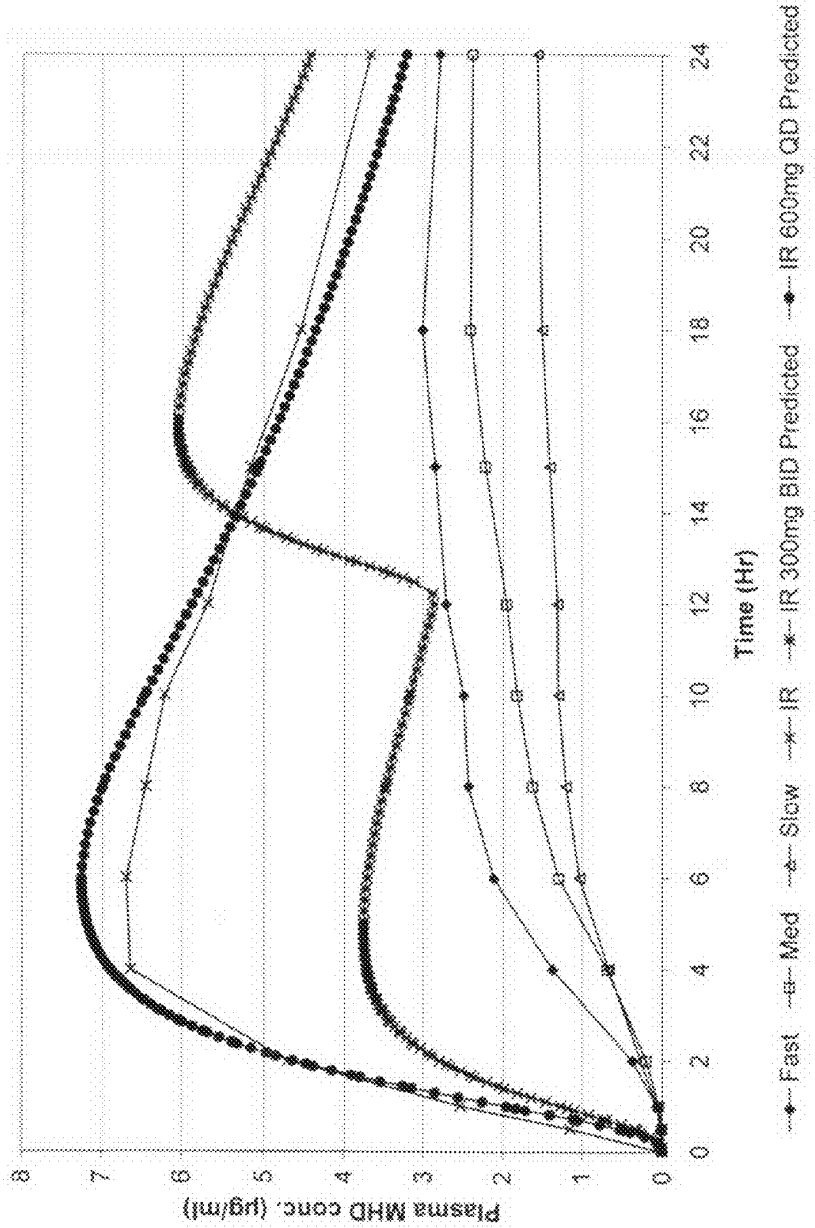

Plasma MHD conc. (µg/ml)
0
1
2
3
4
5
6
7
8
Time (Hr)
0
2
4
6
8
10
12
14
16
18
20
22
24
Fast
Med
Slow
IR
IR 300mg BID Predicted
IR 600mg QD Predicted

FIGURE 10

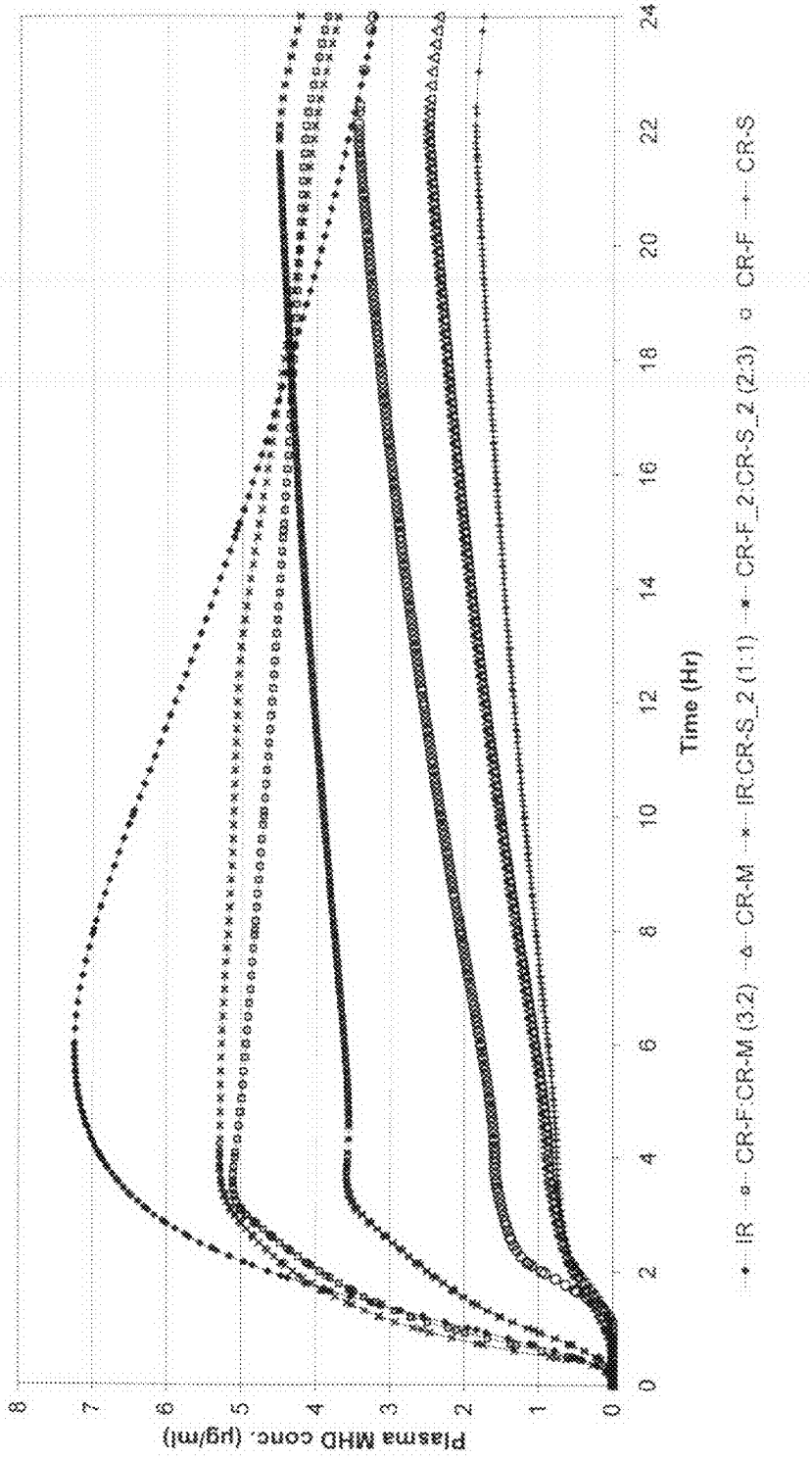

Plasma MHD conc. (µg/ml)
0
1
2
3
4
5
6
7
8
Time (Hr)
0
2
4
6
8
10
12
14
16
18
20
22
24
IR
CR-F:CR-M (3:2)
CR-M
IR:CR-S_2 (1:1)
CR-F_2:CR-S_2 (2:3)
CR-F
CR-S

FIGURE 11

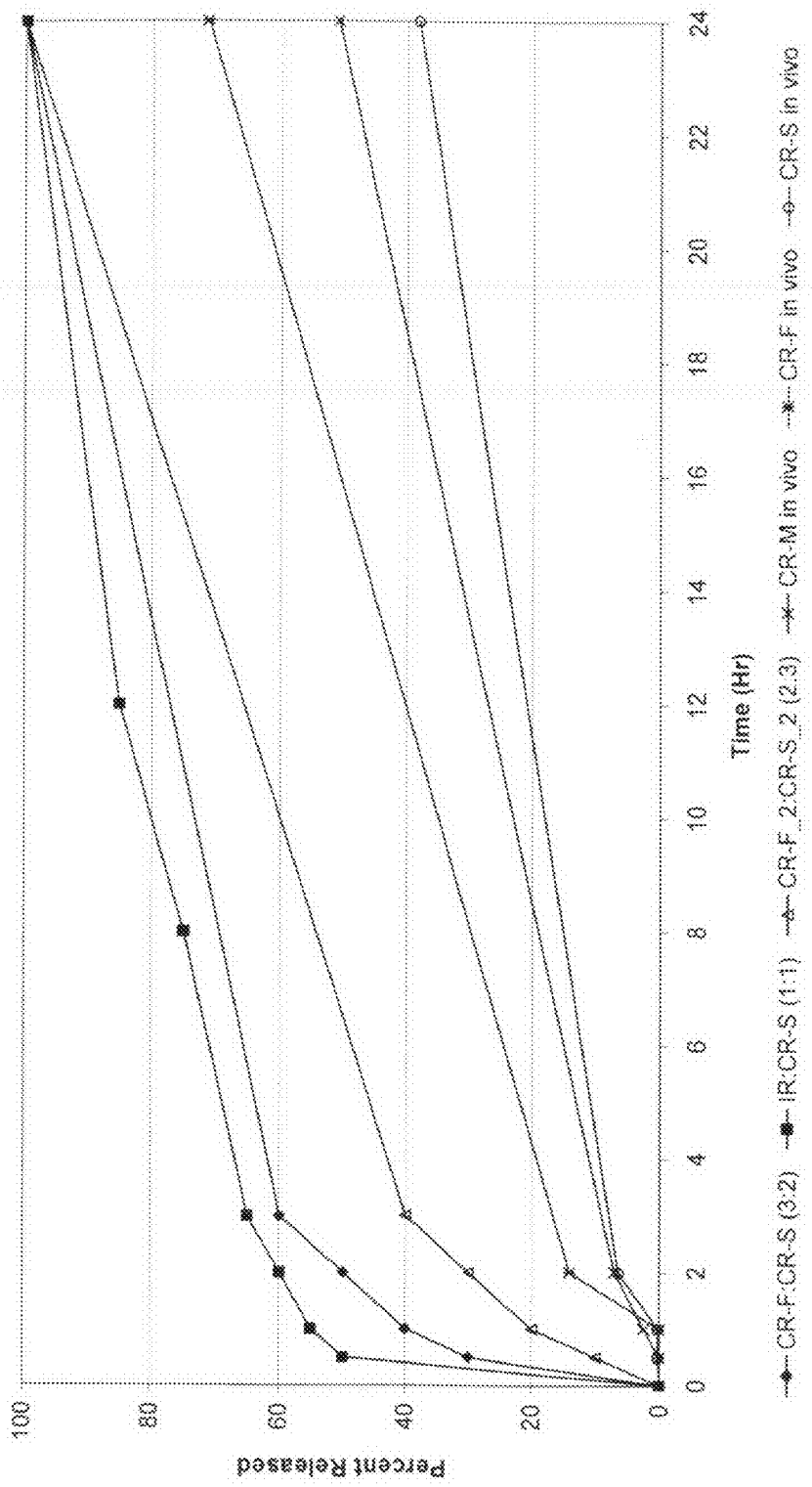

Percent Released
0
20
40
60
80
100
Time (Hr)
0
2
4
6
8
10
12
14
16
18
20
22
24
CR-F:CR-S (3:2)
IR:CR-S (1:1)
CR-F_2:CR-S_2 (2:3)
CR-M in vivo
CR-F in vivo
CR-S in vivo

FIGURE 12

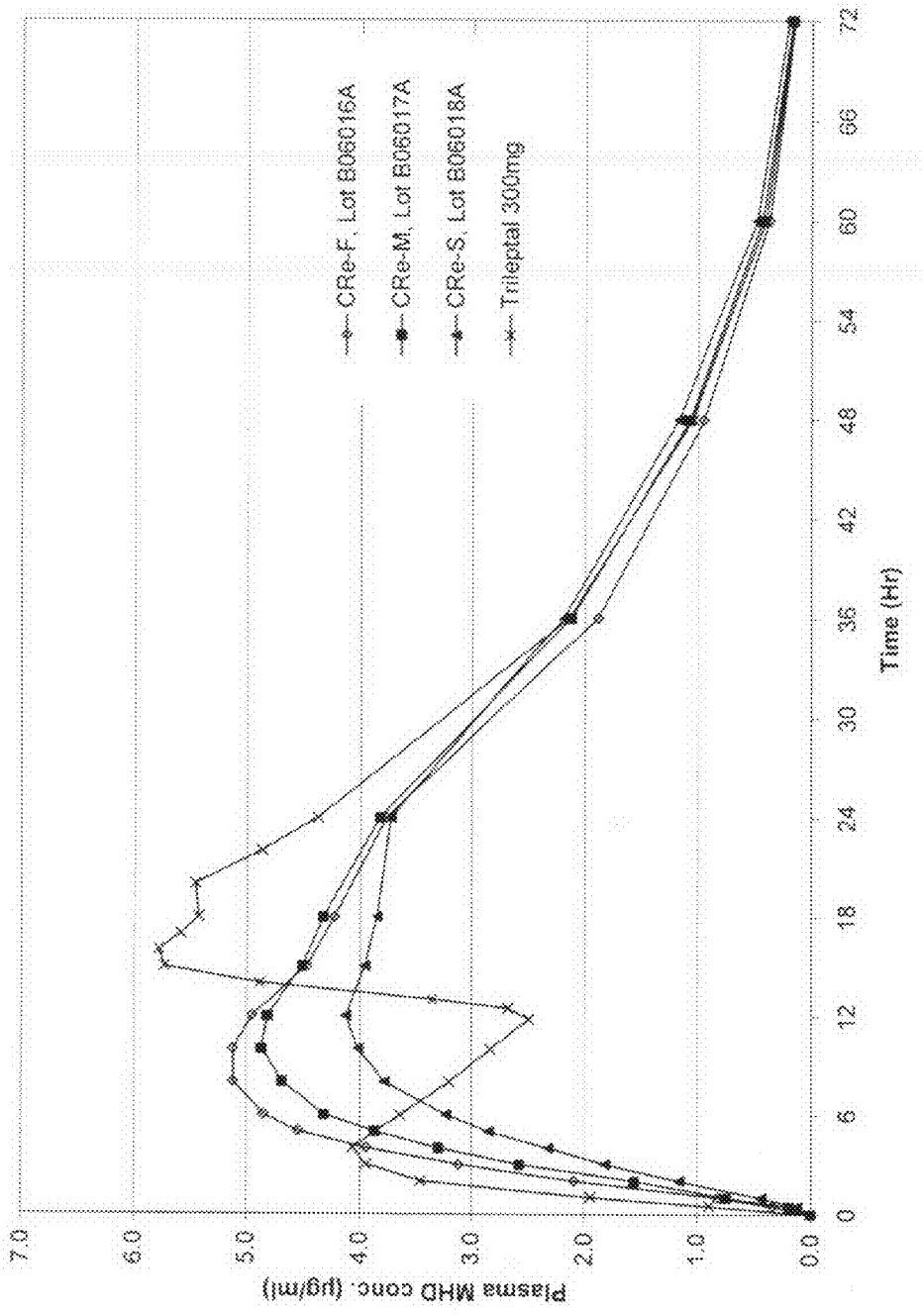

CRe-F, Lot B060016A
CRe-M, Lot B060017A
CRe-S, Lot B060018A
Trileptal 300mg
Plasma MHD conc. (µg/ml)
Time (Hr)
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
0
6
12
18
24
30
36
42
48
54
60
66
72

FIGURE 13

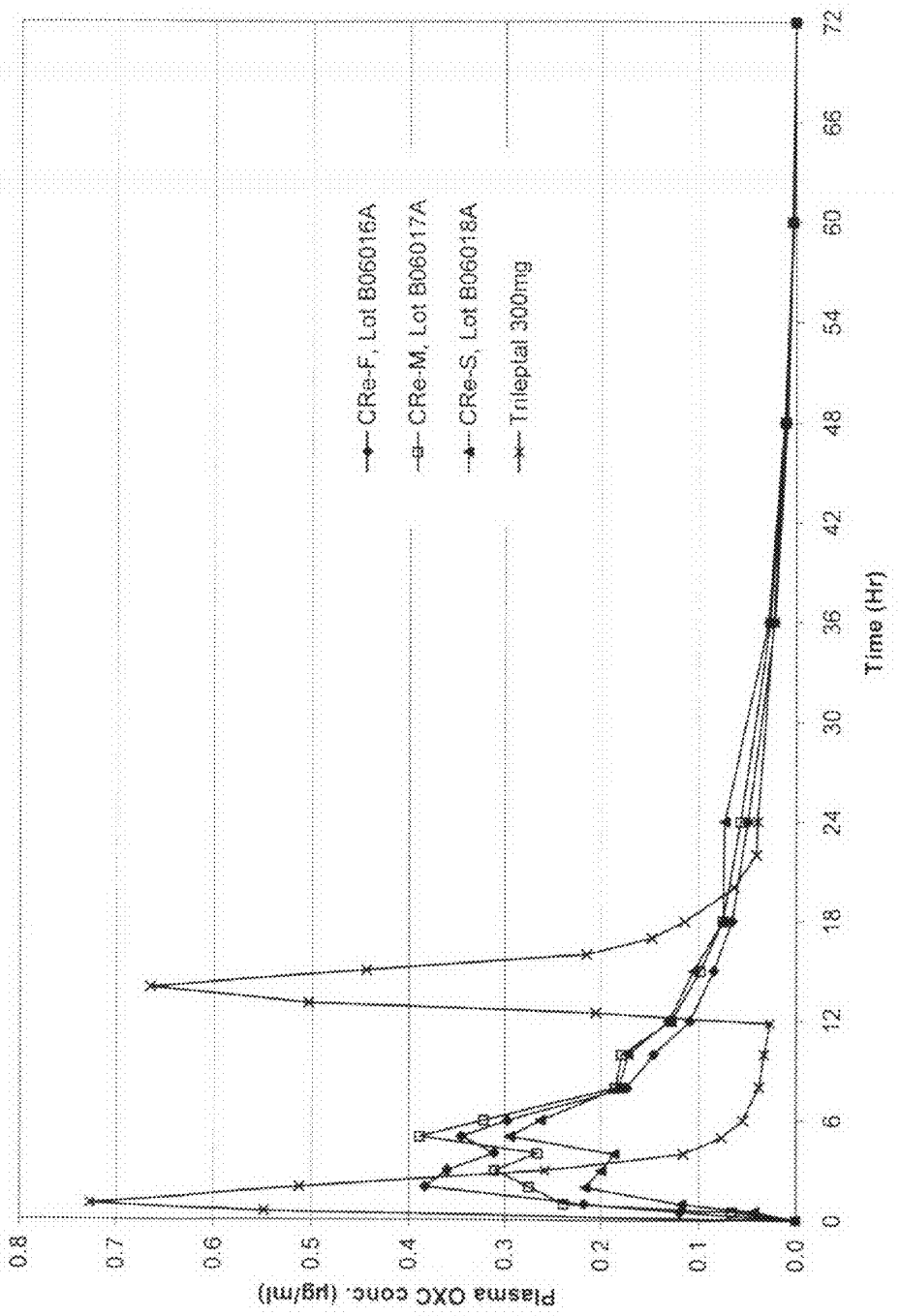
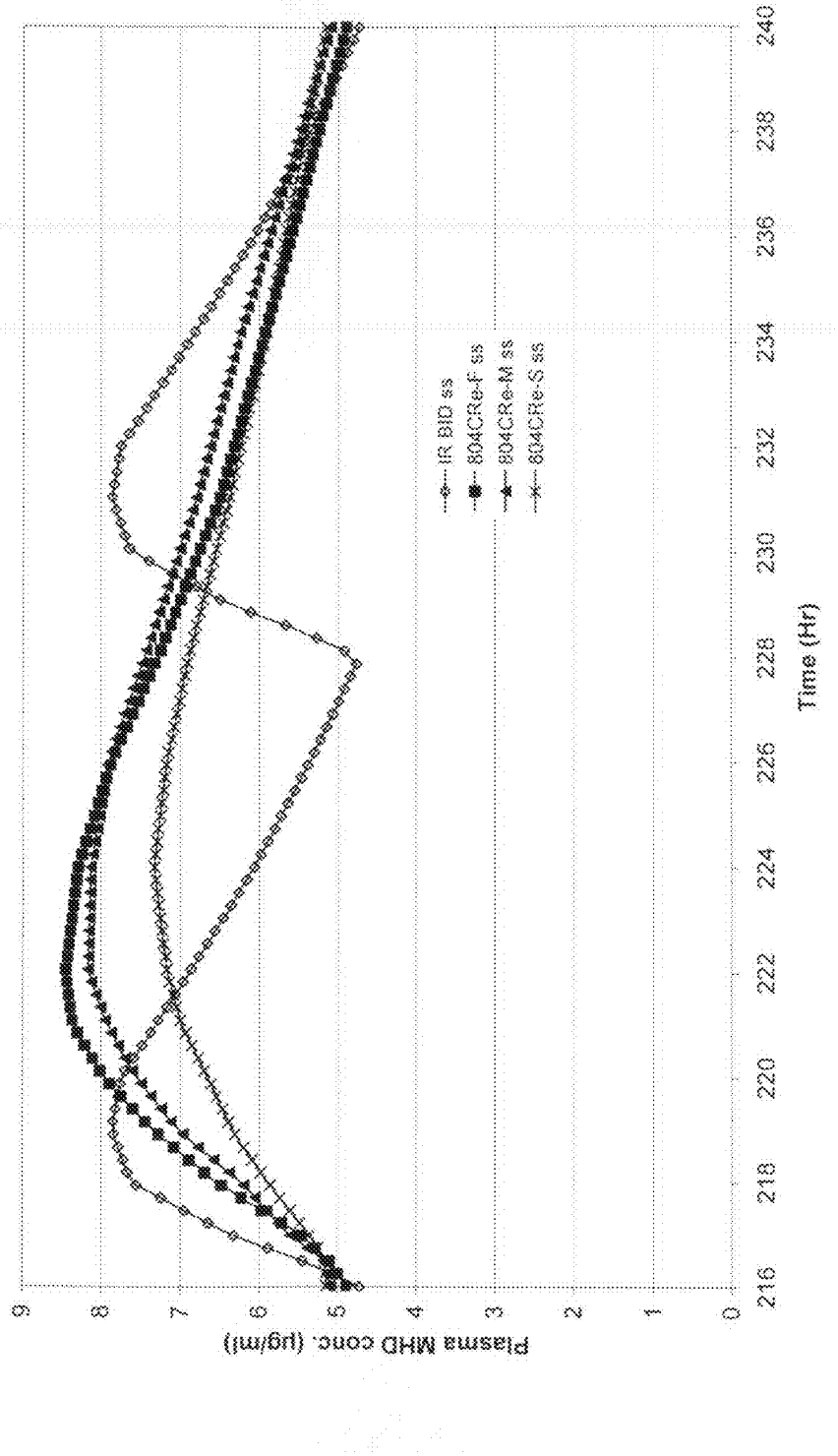

CRe-F, Lot B06016A
CRe-M, Lot B06017A
CRe-S, Lot B06018A
Trileptal 300mg
Plasma OXC conc. (µg/ml)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
Time (Hr)
0
6
12
18
24
30
36
42
48
54
60
66
72

FIGURE 14


Plasma MHD conc. (µg/ml)
0
1
2
3
4
5
6
7
8
9
Time (Hr)
216
218
220
222
224
226
228
230
232
234
236
238
240
IR BID ss
804CRe-F ss
804CRe-M ss
804CRe-S ss

METHOD OF TREATING SEIZURES USING MODIFIED RELEASE FORMULATIONS OF OXCARBAZEPINE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of U.S. application Ser. No. 11/734,874, filed Apr. 13, 2007, which claims priority to U.S. Provisional Application No. 60/794,837, filed Apr. 26, 2006, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention is directed to controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration.

BACKGROUND OF THE INVENTION

Oxcarbazepine belongs to the benzodiazepine class of drugs and is registered worldwide as an antiepileptic drug. Oxcarbazepine is approved as an adjunct or monotherapy for the treatment of partial seizures and generalized tonic-clonic seizures in adults and children. An immediate-release (IR) formulation of oxcarbazepine is currently on the market under the trade name Trileptal® and is administered twice a day to control epileptic seizures. Such immediate release compositions provide the drug to the patient in a manner that result in a rapid rise of the plasma drug concentration followed by a rapid decline. This sharp rise in drug concentration can result in side effects, and make multiple daily administration of the drug necessary in order to maintain a therapeutic level of the drug in the body. The need for a controlled-release dosage form for drugs taken chronically such as oxcarbazepine and derivatives is self-evident. Patient compliance is greatly improved with controlled-release (CR) dosage forms that are taken, for example, once-a-day. Also, there are significant clinical advantages such as better therapeutic efficacy as well as reduced side effects with controlled-release dosage forms.

Oxcarbazepine and its derivatives contemplated in this invention are poorly soluble in water. Due to their poor solubility, their release from a sustained release dosage form is rather incomplete. Whereas the in vitro release of oxcarbazepine is dependent on the dissolution method, including the dissolution media used, it has been found through in silico modeling that the release of oxcarbazepine in vivo from a traditional sustained-release dosage form is relatively low. This results in reduced bioavailability of the drug making the dosage form ineffective in providing a therapeutically effective concentration in the body. This poses a serious challenge to the successful development of sustained-release dosage forms for oxcarbazepine and its derivatives.

The rate of drug release from a dosage form has a significant impact on the therapeutic usefulness of the drug and its side effects. Hence, drug release profiles must be customized to meet the therapeutic needs of the patient. An example of a customized release profile is one that exhibits a sigmoidal release pattern, characterized by an initial slow release followed by fast release which is then followed by slow release until all of the drug has been released from the dosage form.

Sustained-release dosage forms for oxcarbazepine and derivatives have been described in the art. For example, Katzhendler et al. (U.S. Pat. No. 6,296,873) describes sustained-release delivery systems for carbamazepine and its derivatives. Katzhendler et al. teaches that a zero-order release profile is achieved for carbamazepine and derivatives through the use of hydrophilic and hydrophobic polymers. Zero-order (constant) release was achieved using high molecular weight hydroxypropyl methyl cellulose (HPMC) along with some optional hydrophobic excipients. A similar approach is taught by Shah et al. (US Patent Application 20020169145). Franke et al. (US Patent Application 20040142033) discloses sustained-release formulations of oxcarbazepine that are characterized by the release of 55%-85% of the drug in 15 minutes, and up to 95% in 30 minutes. According to the authors, such release profiles provide adequate sustained-release to achieve once-a-day administration of oxcarbazepine. However, the solubility and bioavailability of the drug from these enhanced preparations suitable for once-a-day administration. The prior art does not teach how to make preparations of oxcarbazepine and derivatives characterized by sigmoidal release profiles.

SUMMARY OF THE INVENTION

It is an object of this invention to provide controlled-release formulations of oxcarbazepine for once-a-day administration. The composition of this invention is administered once-a-day and yet meets the therapeutic need of the patient. It is another object of this invention to improve the bioavailability of oxcarbazepine and derivatives thereof. It is yet another object of this invention to meet the therapeutic need of the patient without causing "spikes" in blood drug concentration that may lead to toxicity. It is yet another object of this invention to keep the blood concentration of the drug within the therapeutic window. It is yet another object of this invention to minimize the fluctuation between the C_{max} and C_{min} that is typical of many immediate-release and sustained-release preparations.

Many, if not all, of these objectives may be achieved in this invention through formulations that comprise both solubility-enhancing agents and release-promoting agents, and are characterized by release profiles that meet the requirement for once-a-day administration. The objectives may also be achieved through the combination of a multiplicity of units with different release profiles in one dosage unit. Minipellets/granules/tablets, which can be mixed in a certain ratio, provide a dosage form that meets the above stated therapeutic objectives.

This invention also pertains to multi-layer tablets. Multi-layer tablets can be prepared with each layer releasing the drug at a rate that is different from the rate of release from another layer. In multi-layer tablets, each layer may or may not be coated.

All of the advantages that stem from once-daily administration of a drug apply to the compositions of this invention. Some of the specific advantages of this invention may be: reduced fluctuation between C_{max} and C_{min} during the course of treatment and hence better therapeutic profile, reduced side-effects, improved patient compliance, and improved bioavailability of the drug.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the dissolution profiles for the three exemplary (CR-F, CR-M, and CR-S) oxcarbazepine formulations containing no solubility/release enhancer. The profiles show a non-zero order release with a lag. The T_{80}s (time for 80% of the dose to be released in vitro) for the CR-F, CR-M, and CR-S formulations were 2 Hrs, 5 Hrs and 11 Hrs, respec-

tively. USP Apparatus II at 60 RPM was used. Dissolution medium was 1% SLS in water.

FIG. **2** shows the human pharmacokinetic (PK) profiles with respect to oxcarbazepine for the three exemplary controlled-release formulations of example 1 versus an immediate-release reference product (Trileptal® 600 mg). The strength of each formulation is 600 mg oxcarbazepine per tablet.

FIG. **3** shows the PK profiles with respect to the metabolite of oxcarbazepine (MHD) for the three exemplary controlled-release formulations of example 1 versus an immediate-release reference product (Trileptal® 600 mg). The strength of each formulation is 600 mg oxcarbazepine per tablet.

FIG. **4** shows the solubility results of oxcarbazepine with selected excipients.

FIG. **5** shows the dissolution profiles of oxcarbazepine CR formulations with solubility enhancer (CRe), without solubility enhancer (CR) and a "fast formulation" (CR-F) developed in Example 1. The time to dissolve 80% of the drug (T_{80}) for CRe, CR, and CR-F are 5-6 Hrs, 8 Hrs, and 1.5 Hrs, respectively.

FIG. **6** shows the dissolution profiles for the fast (CRe-F), medium (CRe-M), and slow (CRe-S) oxcarbazepine formulations containing solubility/release enhancers. The T_{80}s for the CRe-F, CRe-M, and CRe-S are 1.5 Hrs, 5 Hrs, and 8 Hrs, respectively. USP Apparatus II at 60 RPM was used. Dissolution medium was 1% SLS in water.

FIG. **7** shows the canine pharmacokinetic profiles with respect to oxcarbazepine, comparing the enhanced formulation (CRe) with non-enhanced formulations containing oxcarbazepine (CR and CR-F).

FIG. **8** shows the canine pharmacokinetic profiles with respect to MHD, comparing the enhanced formulation (CRe) with non-enhanced formulations containing oxcarbazepine (CR and CR-F).

FIG. **9** shows the PK profiles shown in FIG. **8** with in silico predicted PK profile for a twice-a-day 300 mg IR.

FIG. **10** shows in silico predicted PK profiles for various in vitro release profiles.

FIG. **11** shows the in silico predicted in vivo release profiles for the systems in FIG. **10**.

FIG. **12** shows human plasma concentration vs. time profiles with respect to MHD of the three Oxcarbazepine CR formulations in Example 4 (CRe-F, CRe-M, CRe-S) and Trileptal® as an IR control, dosed BID.

FIG. **13** shows human plasma concentration vs. time profiles with respect to the oxcarbazepine of the three Oxcarbazepine CR formulations in Example 4 (CRe-F, CRe-M, CRe-S) and Trileptal® as an IR control, dosed BID.

FIG. **14** shows the in silico predicted steady-state plasma profiles for the three exemplary formulations (CRe-F, CRe-M, and CRe-S) described in Example 4.

DETAILED DESCRIPTION OF THE INVENTION

It is the object of this invention to provide controlled-release oxcarbazepine formulations suitable for once-a-day administration. It is an additional object of the invention to incorporate a combination of solubility-enhancing excipients and/or release-promoting agents into the formulations to enhance the bioavailability of oxcarbazepine and its derivatives. Such compositions are referred to as enhanced formulations.

Oxcarbazepine was formulated to provide release profiles characterized by slow release initially, followed by rapid release and then followed by another period of slow release. Such a release profile is known to those skilled in the art as sigmoidal. Oxcarbazepine formulations with sigmoidal release profiles were tested in human pharmacokinetic (PK) studies. Based on the human data, improvements were made to the formulations by incorporating solubility enhancers and/or release-promoting excipients (such formulation are referred to as enhanced formulations). The enhanced formulations were tested in canine models and were surprisingly found to provide significant increase in bioavailability of oxcarbazepine compared to formulations containing no solubility/release enhancing excipients.

The incorporation of solubility enhancing agents in formulations containing poorly soluble drugs such as oxcarbazepine has a profound effect on the in vivo solubility and hence bioavailability of the drugs. Enhancing the solubility of oxcarbazepine results in an increase in its bioavailability and hence in better therapeutic performance of the drug. A combination of solubility and release promoters is contemplated in this invention. Preferable release promoting agents are pH dependent polymers, also known as enteric polymers. These materials are well known to those skilled in the art and exhibit pH dependent solubility such that they dissolve at pH values higher than about 4.0, while remaining insoluble at pH values lower than 4.0. Solubilizers function by increasing the aqueous solubility of a poorly soluble drug. When a formulation containing both the enteric polymer and solubilizer is exposed to an aqueous media of pH higher than 4.0, the enteric polymer dissolves rapidly leaving a porous structure, resulting in increased contact surface between the aqueous medium and the poorly soluble drug. This increased surface area enhances the efficiency of the solubilizer(s), and hence, the overall solubility and release rate of the drug is enhanced to a point where it impacts the availability of the drug for systemic absorption in patients.

Excipients that function as solubility enhancers can be ionic and non-ionic surfactants, complexing agents, hydrophilic polymers, pH modifiers, such as acidifying agents and alkalinizing agents, as well as molecules that increase the solubility of poorly soluble drug through molecular entrapment. Several solubility enhancers can be utilized simultaneously. All enteric polymers that remain intact at pH value lower than about 4.0 and dissolve at pH values higher than 4.0, preferably higher than 5.0, most preferably about 6.0, are considered useful as release-promoting agents for this invention.

Suitable pH-sensitive enteric polymers include cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic monoester copolymer, methyl acrylate-methacrylic acid copolymer, methacrylate-methacrylic acid-octyl acrylate copolymer, etc. These may be used either alone or in combination, or together with the polymers other than those mentioned above. Preferred enteric polymers are the pharmaceutically acceptable methacrylic acid copolymers. These copolymers are anionic polymers based on methacrylic acid and methyl methacrylate and, preferably, have a mean molecular weight of about 135000. A ratio of free carboxyl groups to methyl-esterified carboxyl groups in these copolymers may range, for example, from 1:1 to 1:3, e.g. around 1:1 or 1:2. Such polymers are sold under the trade name Eudragit™ such as the Eudragit L series e.g. Eudragit L 12.5™, Eudragit L 12.5P™, Eudragit L100™, Eudragit L 100-55™, Eudragit L-30D™, Eudragit L-30 D-55™, the Eudragit S™ series e.g. Eudragit S 12.5™, Eudragit S 12.5P™, Eudragit S100™. The release promoters are not limited to pH dependent polymers. Other hydrophilic

molecules that dissolve rapidly and leach out of the dosage form quickly leaving a porous structure can be also be used for the same purpose.

The release-promoting agent can be incorporated in an amount from 10% to 90%, preferably from 20% to 80% and most preferably from 30% to 70% by weight of the dosage unit. The agent can be incorporated into the formulation either prior to or after granulation. The release-promoting agent can be added into the formulation either as a dry material, or it can be dispersed or dissolved in an appropriate solvent, and dispersed during granulation.

Solubilizers preferred in this invention include surface active agents such as sodium docusate, sodium lauryl sulfate, sodium stearyl fumarate, Tweens® and Spans (PEO modified sorbitan monoesters and fatty acid sorbitan esters), poly(ethylene oxide)-polypropylene oxide-poly(ethylene oxide) block copolymers (aka Pluronics™); complexing agents such as low molecular weight polyvinyl pyrrolidone and low molecular weight hydroxypropyl methyl cellulose; molecules that aid solubility by molecular entrapment such as cyclodextrins, and pH modifying agents, including acidifying agents such as citric acid, fumaric acid, tartaric acid, and hydrochloric acid; and alkalizing agents such as meglumine and sodium hydroxide.

Solubilizing agents typically constitute from 1% to 80% by weight, preferably from 1% to 60%, more preferably from 1% to 50%, of the dosage form and can be incorporated in a variety of ways. They can be incorporated in the formulation prior to granulation in dry or wet form. They can also be added to the formulation after the rest of the materials are granulated or otherwise processed. During granulation, solubilizers can be sprayed as solutions with or without a binder.

This invention also contemplates controlled-release formulations comprising oxcarbazepine that release the drug at variable rates in the GI tract. It is also an object of this invention to design a drug delivery system to deliver drug at a very low rate early, followed by a relatively increased rate. It is another object of this invention to provide a drug release profile that is characterized by an immediate-release followed by a modified-release, such as extended-release (XR) or delayed-release (DR). These types of release profiles ensure that the C_{max} (maximum concentration of the drug in blood/plasma) is kept within the therapeutic window while extending the maintenance of an effective drug level in the body. The goal of this invention is to develop a controlled-release pharmaceutical composition of oxcarbazepine that provides steady-state blood levels of MHD, an active metabolite of oxcarbazepine, at a concentration of about 2 μg/ml to about 10 μg/ml. In the preferred embodiment, steady-state blood C_{max} levels of MHD fall in the range of about 6 μg/ml to about 10 μg/ml, and C_{min} levels of MHD fall in the range of about 2 μg/ml to about 5 μg/ml. Reduced fluctuation between C_{max} and C_{min} during the course of treatment results in a better therapeutic profile, reduced side-effects, improved patient compliance, and improved bioavailability of the drug.

The desired drug release pattern contemplated by this invention is achieved by using "matrix" polymers that hydrate and swell in aqueous media, such as biological fluids. As these polymers swell, they form a homogenous matrix structure that maintains its shape during drug release and serves as a carrier for the drug, solubility enhancers and/or release promoters. The initial matrix polymer hydration phase results in slow-release of the drug (lag phase). Once the polymer is fully hydrated and swollen, the porosity of the matrix increases due to the leaching out of the pH-dependent release promoters, and drug is released at a faster rate. The rate of the drug release then becomes constant, and is a function of drug diffusion through the hydrated polymer gel.

Thus, the release vs. time curve is characterized by at least two slopes: one slope for the lag phase where drug release rate is low and a second slope where drug release is faster. The slope of the rising part of the release vs. time curve can be customized as to match the rate at which the drug is eliminated from the body. A desired release profile can be achieved by using swellable polymers alone or in combination with binders, such as gelling and/or network forming polymers.

The water-swellable, matrix forming polymers useful in the present invention are selected from a group comprising cellulosic polymers, such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), methylcellulose (MC), powdered cellulose such as microcrystalline cellulose, cellulose acetate, sodium carboxymethylcellulose, calcium salt of carboxymethylcellulose, and ethylcellulose; alginates, gums such as guar and xanthan gums; cross-linked polyacrylic acid derivatives such as Carbomers (aka Carbopol™) available in various molecular weight grades from Noveon Inc. (Cinncinatti, Ohio); carageenan; polyvinyl pyrrolidone and its derivatives such as crospovidone; polyethylene oxides; and polyvinyl alcohol. Preferred swellable polymers are the cellulosic compounds, HPMC being the most preferred.

The swellable polymer can be incorporated in the formulation in proportion from 1% to 50% by weight, preferably from 5% to 40% by weight, most preferably from 5% to 20% by weight. The swellable polymers and binders may be incorporated in the formulation either prior to or after granulation. The polymers can also be dispersed in organic solvents or hydro-alcohols and sprayed during granulation.

It is yet another aspect of this invention to prepare formulations of oxcarbazepine that combine multiple modified-release "units," each "unit" prepared according to any one or more of the above-disclosed dosage forms, to provide for a customized release profile.

The modified-release units comprise minipellets/granules/tablets etc., each with unique release profiles, that can be mixed in a certain ratio to provide a dosage form that meets the above-stated therapeutic objectives. Alternatively, multiple modified release units may be formed into of multi-layer tablets. Multi-layer tablets can be prepared with each layer releasing the active compound at a rate that is different from the rate of release of the active ingredient from another layer. In multi-layer tablets, each layer may optionally be coated with controlled-release polymer(s). The combination dosage forms can exhibit release profiles that comprise any/all possible combinations of immediate release (IR), delayed release (DR), and extended release (XR) formulations. Pellets/granules/tablets or each layer of a single tablet may optionally be coated.

Various hydrophobic excipients can be used to modify the hydration rate of the dosage unit when exposed to water or aqueous media. These excipients retard the wetting of the dosage unit and hence modify the release of the active agent. Hydrophobic excipients suitable for this invention are represented by, but not limited to, glyceryl monstearate, mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex, Eastman Fine Chemical Company), glycerylmonooleate, a mixture of mono, di and tri-glycerides (ATMUL 84S), glycerylmonolaurate, glyceryl behenate, paraffin, white wax, long chain carboxylic acids, long chain carboxylic acid esters and long chain carboxylic acid alcohols.

Examples of saturated straight chain acids, useful with the invention, are n-dodecanoic acid, n-tetradecanoic acid, n-hexadecanoic acid, caproic acid, caprylic acid, capric acid,

lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid and melissic acid. Also useful are unsaturated monoolefinic straight chain monocarboxylic acids. Examples of these are oleic acid, gadoleic acid and erucic acid. Also useful are unsaturated (polyolefinic) straight chain monocarboxylic acids such as linoleic acid, linolenic acid, arachidonic acid and behenolic acid. Useful branched acids include, for example, diacetyl tartaric acid.

Examples of long chain carboxylic acid esters include, but are not limited to: glyceryl monostearates; glyceryl monopalmitates; mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex 600, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monooleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate and glyceryl monolinoleate (Myverol 18-92, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monogadoleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate, glyceryl monolinoleate, glyceryl monolinoleate and glyceryl monogadoleate (Myverol 18-99, Eastman Fine Chemical Company); acetylated glycerides such as distilled acetylated monoglycerides (Myvacet 5-07, 7-07 and 9-45, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company), d-alpha tocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS, Eastman Chemical Company); mixtures of mono- and diglyceride esters such as Atmul (Humko Chemical Division of Witco Chemical); calcium stearoyl lactylate; ethoxylated mono- and di-glycerides; lactated mono- and di-glycerides; lactylate carboxylic acid ester of glycerol and propylene glycol; lactylic esters of long chain carboxylic acids; polyglycerol esters of long chain carboxylic acids, propylene glycol mono- and di-esters of long chain carboxylic acids; sodium stearoyl lactylate; sorbitan monostearate; sorbitan monobleate; other sorbitan esters of long chain carboxylic acids; succinylated monoglycerides; stearyl monoglyceryl citrate; stearyl heptanoate; cetyl esters of waxes; cetearyl octanoate; C_{10}-C_{30} cholesterol/lavosterol esters; and sucrose long chain carboxylic acid esters. In addition, waxes can be useful alone or preferably in combination with the materials listed above. Examples of these are white wax, paraffin and carnauba wax.

Drug, polymers, and other excipients are typically combined and wet granulated using a granulating fluid. However, other methods of forming granules such as slugging, and roller compaction can also be used to manufacture matrix granules. Matrix tablets can also be made by direct compression. In wet granulation, typical granulating fluids are: water, a mixture of water and alcohol, anhydrous alcohol. Wet granules can be made in any granulating device such as mixers, high shear granulators, and fluid bed granulators. Granules can be dried in appropriate drying equipment such as fluid bed dryers, ovens, microwave dryers etc. Granules can also be air-dried. Dried granules can be milled using appropriate milling device to achieve a particular particle size distribution. Granules can be filled in to capsules, or blended with other excipients and tableted on a tablet press. Granules can also be packaged into sachets for sprinkle application. Other excipients used to aid tableting are well known to those skilled in the art and include magnesium stearate, talc, cabosil etc. Granules and tablets can, optionally, be coated to further modify release rates. Furthermore, formulations can also optionally contain dyes.

Optionally, but preferably, the tablet composition can contain one or more lubricants, which may be added to assure proper tableting. Non-limiting examples of lubricants include magnesium stearate, calcium stearate, zinc stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, sodium stearyl fumarate, hydrogenated vegetable oils, and other waxes, including but not limited to, beeswax, carnuba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, and stearyl alcohol. The lubricant, when present, is typically included in an amount of from about 0.1 wt. % to about 20 wt. % of the composition, preferably from about 1 to about 10 wt. %, and more preferably about 0.3 to about 3.0 wt. %.

The oxcarbazepine dosage can be formulated into tablets, granules, and pellets. The steps involved in the manufacturing of these dosage forms are well known to those skilled in the art. Briefly, tablets can be compressed from directly compressible blend containing the active or pre-formed granules. The tablets can be coated or not coated. The coating may optionally impart modification of release. Granules can be made by high shear granulation or fluid bed processing. The granules may or may not be coated. Pellets can be manufactured by drug layering on inert carriers such as sugar spheres. Pellets can also be manufactured by extrusion/spheronization process. The pellets may or may not be coated. Coated pellets and granules can be filled into capsules.

Formulations of this invention can also be made in pelletized forms, which can be filled into capsules or dispensed in sachets for sprinkle application. Each pellet is composed of the drug, swellable polymer(s) and other excipients that aid the processing. Pellets can be prepared in one of the many ways that are known by those skilled in the art. These include, for example, extrusion/spheronization and roller compaction (slugging). In the extrusion/spheronization technique, drug is mixed with swellable polymer(s), such as cellulosic polymers and other excipients. The blend is then granulated in a high shear granulator. The wet mass is then passed through an extruder and spheronized using a spheronizer. The pellets are then dried in an oven or fluid bed processor. The dried pellets are either processed further or encapsulated without further processing.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The invention now will be described in particularity with the following illustrative examples; however, the scope of the present invention is not intended to be, and shall not be, limited to the exemplified embodiments below.

EXAMPLES

Example 1

Oxcarbazepine Formulations with Sigmoidal Release Profiles

Table 1 provides the formula composition of oxcarbazepine controlled-release preparations with sigmoidal release profiles. Granules were prepared by high shear granulation using anhydrous ethanol as the granulating liquid. All ingredients, except for magnesium stearate, were charged in to VG-65/10M high shear granulator. The dry powders are

blended by running the blade for 3 minutes, after which time the anhydrous ethanol was sprayed onto the mixing blend at a spray rate of approximately 40-60 gm/min. After about a minute of spray, the chopper on the VG-65/10M was started and run throughout the spray. Once the granulation was completed, the granulation was discharged from the VG high shear granulator, spread on an appropriate tray and placed in an oven to dry at 40° C. for 24 Hrs. Alternatively, granules can be dried using a fluid bed processor. Dry granules were screened through an 18-mesh screen. Screened granules were blended with magnesium stearate in a proportion of 99.5% granules and 0.5% magnesium stearate. The blend was then tableted on a rotary tablet press.

TABLE 1

Formula composition of Oxcarbazepine CR formulations with changing slope

Ingredients	SLI 530 CR-F (Fast)	SLI530 CR-M (Medium)	SLI530 CR-S (Slow)
Oxcarbazepine	60	60	60
Compritol 888ATO	9.5	7	—
Prosolv HD90	9.8	20.3	15
Kollidon 25	10	—	—
Kollidon 90	—	3	—
Methocel E5 Prem. LV	—	—	10
Methocel K4M Premium CR	—	—	5
Carbopol 971P	10	9	9
Mg Stearate	0.5	0.5	0.5
FD&C Red #40	—	—	0.5
FD&C Blue #1	0.2	—	—
FD&C Yellow #6	—	0.2	—
Anhydrous Ethanol	*	*	*
Total	100	100	100

* Removed during processing

FIG. **1** shows the dissolution profiles of three exemplary oxcarbazepine CR formulations (CR-F, CR-M, and CR-S). The profiles exhibited non-zero order release.

Example 2

Human Pharmacokinetic Evaluation of Oxcarbazeine CR Formulations from Example 1

The three formulations from the Example 1 were evaluated in humans to obtain pharmacokinetic information. An immediate release tablet (Trileptal® 600 mg) was used as a control reference. The formulations were examined in a randomized, single dose, crossover study in healthy human volunteers. Blood samples were analyzed for both the parent molecule oxcarbazepine and its metabolite (the monohydroxy derivative, MHD).

Table 2 provides the mean PK parameters for MHD. The PK profiles are shown in FIGS. **2** and **3**.

TABLE 2

Pharmacokinetic parameters of the three exemplary formulations in example 1 and immediate release reference product.

PK Parameters	CR-F Fast	CR-M Med	CR-S Slow	Trileptal ™ IR
T_{max} (Hr)	6.5	8.4	9.1	1.4
C_{max} (ug/mL)	0.248	0.146	0.103	1.412
AUC_{last} (Hr*ug/mL)	3.0	2.5	1.7	5.7
Rel BA	53%	44%	30%	100%

Example 3

Solubility Enhancers Screening

The solubility of oxcarbazepine in the presence of excipients was evaluated as follows:

Excipients were dissolved in phosphate buffer to make solutions with concentrations shown in Table 3. One gram of oxcarbazepine was then mixed with 19 gm of the excipient solution. The mixture was rocked overnight at room temperature and then filtered using 0.22 μm filter. The filtrates were analyzed by HPLC. The solubility results are given in Table 3 and FIG. **4**.

TABLE 3

Solubility of Oxcarbazepine in the presence of excipients

Excipients	Excipient conc. (% w/w)	Solubility (mg/mL)
Phosphate Buffer Control	NA	0.4009
Hydroxypropyl betacyclodextrin (HBCD)	5	1.0218
Sodium Lauryl Sulfate (SLS)	5	4.1113
Kollidon 17	1	0.1717
SLS/HBCD	1, 1	0.3489
Cremophor RH40	1	0.3140
Docusate Sodium	5	6.5524
SLS/Polyethylene Glycol 400 (PEG400)	5, 1	3.0516
SLS/Stearic Acid/PEG400	5, 1, 1	3.2821
De-ionized Water	NA	0.2733

Example 4

Formulation of Enhanced Dosage Forms

Tables 4 and 5 provide the composition of the formulation containing solubility- and release-enhancing agents. Granules were manufactured by high shear granulation using water as the granulating liquid. All ingredients, except for magnesium stearate, were charged into a VG-65/10M high shear granulator. The dry powders were blended by running the blade for 3 minutes, upon which time water was sprayed onto the mixing blend at a spray rate of approximately 40-60 gm/min. After about a minute of spray, the chopper on the VG-65/10M was started and run throughout the spray. Once the granulation was completed, the granulation was discharged from the VG high shear granulator, spread on an appropriate tray and placed in an oven to dry at 40° C. for 24 Hrs. Alternatively, granules can be dried using a fluid bed processor. Dry granules are screened through an 18-mesh screen. Screened granules were blended with magnesium stearate in a proportion of 99.5% granules and 0.5% magnesium stearate. The resulting blend was then tableted on a rotary tablet press. Dissolution profiles for these formulations are shown in FIGS. **5** and **6**.

TABLE 4

Percent Composition of Enhanced (CRe-M) and non-Enhanced (CR) Prototypes

Formulation	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
Oxcarbazepine	60	60
Prosolv SMCC50	10	25
PVP K25	5	5

TABLE 4-continued

Percent Composition of Enhanced (CRe-M) and non-Enhanced (CR) Prototypes

Formulation	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
HPMC K4M premium	10	10
SLS	5	0
Eudragit L100-55	10	0
Magnesium Stearate	0.5	0.5

TABLE 5

Percent Composition for the three exemplary enhanced formulations: CRe-F, CRe-M, and CRe-S.

Formulation	% PD0294-046 CRe-F	% PD0294-051 CRe-M	% PD0294-054 CRe-S
Oxcarbazepine	60	60	60
Prosolv SMCC50	15	10	5
PVP K25	5	5	5
HPMC K4M premium	5	10	15
SLS	5	5	5
Eudragit L100-55	10	10	10
Magnesium Stearate	0.5	0.5	0.5

Example 5

Canine PK Studies on Formulations from Example 4, Table 4 and Example 1. (SLI530CR-F)

Six male beagle dogs were dosed orally with the formulations in the order given in Table 6. Blood was drawn over a 24 Hr period and blood samples were analyzed by HPLC. A noncompartmental analysis of the data was used to generate T_{max}, C_{max}, AUC_{last}, and AUC_{inf}. Relative Bioavailability was calculated in Excel using the AUC_{last} and AUC_{inf} for the CRf formulation as the control. The PK profiles for oxcarbazepine and 10-hydroxycarbazepine are given in FIGS. **7** and **8**.

TABLE 6

Prototypes tested in dogs

Phase	Test Article	SLI Lot #	Dose (mg)
1	Oxcarbazepine CR	PD0294-024A	600
2	Oxcarbazepine CRe	PD0294-024B	600
3	Oxcarbazepine CR-F	B04032	600

TABLE 7

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine

Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CRe-M) PD0294-024B	Fast CR (CR-F) B04032
T_{max}	1.5	1.8	1.7
C_{max}	1.20	1.72	0.7
AUC_{last}	3.44	7.98	3.41

TABLE 7-continued

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine

Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CRe-M) PD0294-024B	Fast CR (CR-F) B04032
AUC_{inf}	3.74	11.09	4.01
Rel BA_{last}	101%	234%	100%
Rel BA_{inf}	93%	276%	100%

Example 6

In Silico Modeling of Various Release Profiles of Oxcarbazepine XR

In silico modeling was carried out for various hypothetical systems. Results are shown in FIGS. **9-11**.

Example 7

Human Pharmacokinetic Evaluation of Solubility Enhanced Oxcarbazepine CR Formulations from Example 4

The three solubility enhanced prototypes from the Example 4 were evaluated in humans to obtain pharmacokinetic information. An immediate release tablet (Trileptal® 300 mg) given BID was used as a reference. The formulations were examined in a randomized, single dose, crossover study in healthy human volunteers. Blood samples were analyzed for both the parent molecule oxcarbazepine and its metabolite (the monohydroxy derivative, MHD).

Table 8 provides the mean PK parameters for MHD. The PK profiles are shown in FIGS. **12** and **13**.

TABLE 8

Pharmacokinetic parameters of the three exemplary solubility enhanced formulations in Example 4 and Trileptal ™

PK Parameters	CRe-F Fast	CRe-M Med	CRe-S Slow	Trileptal ™ BID
T_{max} (Hr)	9	11	14	16
C_{max} (ug/mL)	5.32	5.14	4.40	6.23
AUC_{last} (Hr*ug/mL)	160.3	161.3	148.9	167.1
Rel BA	96%	97%	89%	100%

What is claimed is:

1. A method of treating seizures comprising administering to a subject in need thereof a pharmaceutical formulation comprising a homogeneous matrix comprising:

(a) oxcarbazepine;

(b) a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, crosslinked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;

(c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and

(d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate,

polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, and Eudragit L100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers.

2. The method of claim **1**, wherein the surface active agents comprise sodium docusate, sodium lauryl sulfate, sodium stearyl fumarate, polyethylene oxide (PEO) modified sorbitan monoesters, fatty acid sorbitan esters, polyethylene oxide-polypropylene oxide-(poly(ethylene oxide)) block copolymers, or combinations thereof.

3. The method of claim **1**, wherein the cellulosic polymers are selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), methylcellulose (MC), powdered cellulose, cellulose acetate, sodium carboxymethylcellulose, calcium salt of carboxymethylcellulose, and ethylcellulose.

4. The method of claim **1**, wherein the release promoting agent is incorporated in an amount from 10% to 90% by weight of the formulation, and the agent that enhances the solubility of oxcarbazepine is incorporated in an amount from 1% to 80% by weight of the formulation.

5. The method of claim **4**, wherein the release promoting agent is incorporated in an amount from 30% to 70% by weight of the formulation, and the agent that enhances the solubility of oxcarbazepine is incorporated in an amount from 1% to 80% by weight of the formulation.

6. The method of claim **1**, wherein the amount of oxcarbazepine is effective to produce a steady state blood level of monohydroxy derivative of oxcarbazepine in the range of about 2 μg/ml to about 10 μg/ml.

7. The method of claim **1**, wherein the formulation is effective in minimizing fluctuations between C_{min} and C_{max} of monohydroxy derivative of oxcarbazepine.

8. The method of claim **7**, which provides C_{max} levels of monohydroxy derivative of oxcarbazepine in the range of about 6 μg/ml to about 10 μg/ml and C_{min} levels of monohydroxy derivative of oxcarbazepine in the range of about 2 μg/ml to about 5 μg/ml.

9. The method of claim **1**, wherein the amount of oxcarbazepine in the formulation is 600 mg.

10. The method of claim **1**, wherein the formulation is in the form of pellets, tablets, granules or capsules.

11. The method of claim **10**, wherein the formulation is in the form of tablets.

12. The method of claim **11**, wherein each tablet comprises 600 mg of oxcarbazepine.

13. The method of claim **1**, wherein the matrix-forming polymer is present in the amount of 1% to 50% by weight of the formulation.

14. The method of claim **1**, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, sodium stearyl fumarate, hydrogenated vegetable oils, and waxes.

15. The method of claim **14**, wherein the wax is selected from the group consisting of beeswax, carnuba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, and stearyl alcohol.

16. The method of claim **14**, wherein the lubricant is incorporated in the formulation in an amount of from 0.1% to 20% by weight of the formulation.

17. The method of claim **1**, wherein the polymer having pH-dependent solubility remains intact at pH values of below 4 and dissolves at pH values of more than 4.

18. The method of claim **1**, wherein the polymer having pH-dependent solubility dissolves at pH values of more than 5.

19. The method of claim **1**, wherein the polymer having pH-dependent solubility dissolves at pH values of more than 6.

20. The method of claim **1**, wherein the formulation comprises HPMC and polyvinyl pyrrolidone as matrix-forming polymers; sodium lauryl sulfate as the agent that enhances the solubility of oxcarbazepine, and Eudragit L100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)) as the release promoting agent.

21. The method of claim **1**, wherein the formulation is administered once a day.

22. The method of claim **1**, wherein the seizure is an epileptic seizure.

23. The method of claim **22**, wherein the epileptic seizure is a partial seizure or a generalized tonic-clonic seizure.

24. The method of claim **1**, wherein the patient is an adult or child.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 7,910,131 B2
APPLICATION NO.	: 12/230276
DATED	: March 22, 2011
INVENTOR(S)	: Bhatt et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims:

Col. 14, claim 24, line 41, "patient" should read --subject--.

Signed and Sealed this
Twelfth Day of November, 2013

Teresa Stanek Rea

Teresa Stanek Rea
Deputy Director of the United States Patent and Trademark Office

CERTIFICATE OF FILING AND SERVICE

United States Court of Appeals
for the Federal Circuit

Appeal Nos. 2016-1619, -1621, -1763, -1764

Supernus Pharmaceuticals, Inc. v. Actavis Inc., et al.

I, Maryna Sapyelkina, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by Holland & Knight LLP, Attorneys for Appellants to file and print this document. I am an employee of Counsel Press.

On the **9th Day of May, 2016**, counsel for Appellants has authorized me to electronically file the within **Brief for Defendants-Appellants (Confidential and Non-Confidential versions)** with the Clerk of the Court using the CM/ECF System, which will serve via e-mail notice of such filing to any of the following counsel registered as CM/ECF users:

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On the same day as above, I served two copies of the within Confidential Brief though the Overnight Next Day Air Federal Express, postage prepaid.

Upon acceptance by the Court of the e-filed document, six paper copies of the Confidential version will be filed with the Court, via Federal Express, within the time provided in the Court's rules.

May 9, 2016

/s/ Maryna Sapyelkina
Maryna Sapyelkina
Counsel Press

FORM 19. Certificate of Compliance With Rule 32(a)

Form 19
Rev. 3/16

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

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May 9, 2016

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